Epigenomics AG vs Exact Sciences: the survival of the FITest !

"**For me the biggest payoff in cancer research would be the discovery of biomarkers that can be measured in the blood that reflect the presence of early-stage cancer."**

Dr Leland H. Hartwell, March 2008
President, Fred Hutchinson Cancer Research Center
Nobel Prize in Physiology or Medicine, 2001

Epigenomics AG (EPGNF.PK) recently filed with the FDA the 4th and last module of its blood based colorectal cancer (CRC) screening test, EpiProcolon (EPC). Following the recent successful read-out of the head-to-head study vs. FIT, the stage is set for the first PMA certified blood based cancer screening test mid 2013, and for Dr Hatwell's vision to come true. (Below I shall refer to Epigenomics as ECX, its German local exchange code)

Exact Sciences (EXAS) completed recruitment of the Deep-C pivotal trial for its CRC stool DNA screening test Cologuard in November. The read-out is expected in March/April and PMA approval early 2014. EXAS is well known to the readers of Seeking Alpha, and enjoys a broad analysts' coverage, so I shall limit my comments to the points relevant to the comparison between the two.

Before getting into the thick of it let me start with a couple of warnings: as far as facts are concerned, be aware of the trivial (product distribution), the easily confusing (polyp terminology) more so than of the seemingly complex (DNA methylation). As far as opinions are concerned, be aware of interest groups' interests (big pharma, gastroenterologists etc) and remain suspicious even of "independent" opinions (scientists, KOLs, financial analysts etc), myself included !

Cancer: "the emperor of all maladies"

With USD 64 bn in 2011, and expected to grow above average, the market for cancer therapeutics is already and by far (9%) the largest category of the global therapeutics drugs market. It is 50% bigger than the anti-hypertensives, which is declining, and almost double the size of anti-diabetics, the fastest growing of the top 5 categories, according to EvaluatePharma's most recent World Preview 2018.

In contrast the overall IVD (in-vitro diagnostics) market is less than USD 50 bn, and growing at a slower pace than that of its big brother pharma TRx market. It is also controlled by big pharma as Roche (RHHBY OB), J&J (JNJ) and Abbott (ABT) command the top 4 slots alongside Siemens (SI).
(see the 2011 Diagnostics report by PriceWaterhouseCooper, an excellent and freely available resource for more information about IVD market)

Molecular Diagnostics (MDx) on the other hand is only about a tenth of the IVD market but growing well above 10% annually. Within that hot spot, there is a super hot spot, theranostics (therapeutics + diagnostics) also called companion diagnostics and linked to the concept of personalised medicine. Discoveries in molecular biology have lead to a better understanding of signalling pathways, of how cancer grows, develops resistance, mutates etc. This has lead to a new way of looking at cancer not so much based on the organ affected but on the genetic profile of the tumor cells. This is the fascinating story of Gleevec, nearly dumped by Novartis (NVS) before showing extraordinary results in ABL mutated sub-group of CML patients (a form of leukemia). It got approved in record time by the FDA in 2001 and since then has been approved in 10 different cancer types. Stratifying patients according to their genetic profile is the cheapest, fastest and increasingly only way for big pharma to successfully develop a new anti-cancer drug,
This is the area big pharma is really interested in, by choice and by necessity. Breakthrough in screening or even early detection is the least of their concern.

Why screen for cancer ?

This sounds like an awkward question to ask, but epidemiologists insist that the only outcome of cancer screening should be reduction in mortality rate. If early diagnostic only makes you live longer **with** cancer, but doesn't improve your survival horizon, what's the point ?

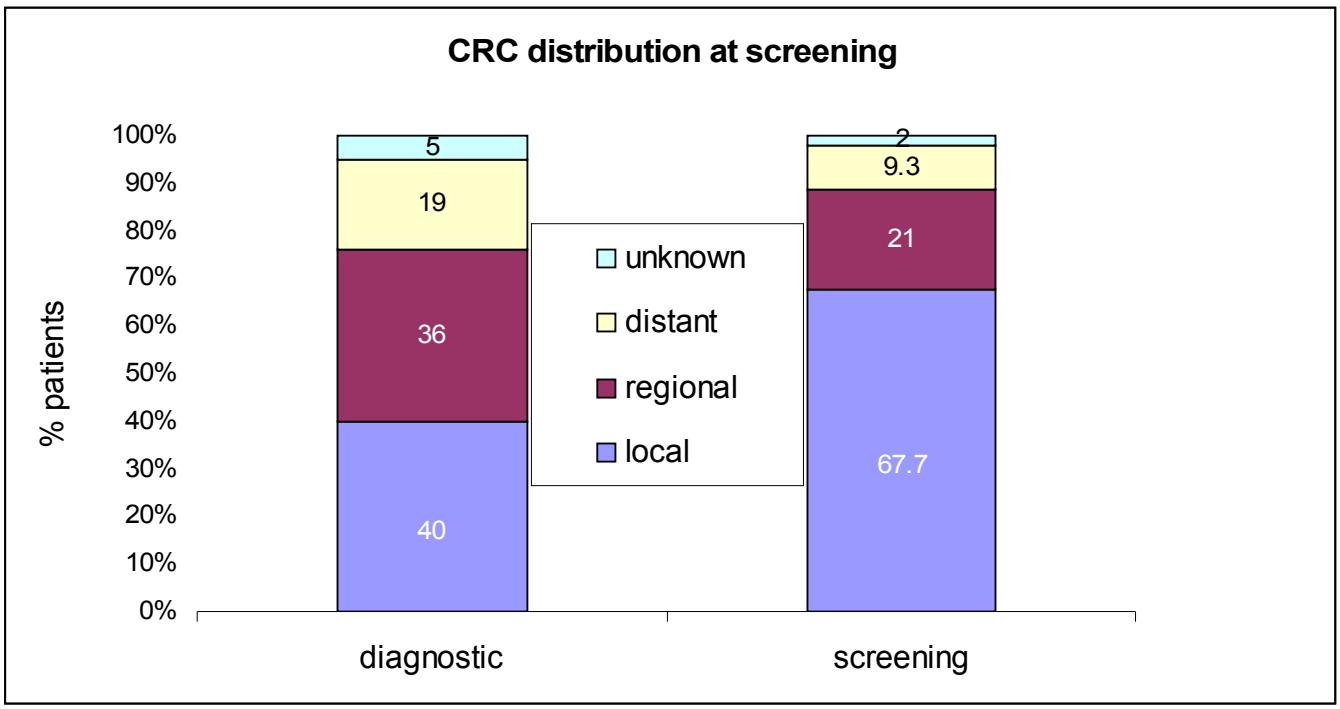
I'd like to refer to an expert for a more detailed and qualified explanation of the underlying concepts: screening, diagnosis, early detection and prevention. It is a lecture by epidemiologist Dr Judith Walsh, from UCSF, given in August 2012. The title says it all "Controversies in cancer screening". The first 28 minutes are dealing with CRC. To me, the most shocking part is not what Dr Walsh reveals, but what she doesn't even mention once: blood-based CRC screening ! I'll come back to this conundrum in a later section.

Of all cancer types, breast cancer has been the first one for which it has been established that screening had an overall survival benefit. Imaging has been and still is the reference technology. With increasing participation and improving technology, over-diagnosis, and as a consequence over-treatment, have taken center stage within the communities of experts (immunologists, radiologists, surgeons, radiotherapists and oncologists) and patients advocacy groups alike.

Prostate cancer testing measuring PSA (Prostate Specific Antigen, an enzyme) from a blood sample, gradually grew into an inofficial but de facto screening program for men.
USPSTF, the most evidence-based society in charge of drafting screening and treatment guidelines recently scrapped PSA testing as a recommended option for all asymptomatic men. This has escalated an already heated controversy. Neither PSA nor FIT (Faecal Immunological Test or iFOBT,immunological Faecal Occult Blood Test) have completed a proper, evidence based PMA (Pre-Market Approval) certification, but are marketed under FDA section 510(k) FDCA, a PMN, Pre-Market Notification. Further readings on the PSA controversy featured in the New York Times.
"US Panel Says No To Prostate Screening For Healthy Men", NYT, Oct 6, 2011
"The Great Prostate Mistake", Op-Ed NYT, March 9, 2010 by Dr Richard Ablin,

Why screen for colorectal cancer ?

Evidence as to the benefit of screening for CRC is very clear cut, whatever the diagnostic method used (colonoscopy, sigmoidoscopy, FOBT/FIT). Even FOBT has a significant positive impact, although its detection rate is the lowest of all recommended methods. It is mainly the development stage of the tumor at the timing of the diagnostic which conditions the 5 years survival chances.



Pre-cancerous polyps	Early stage cancer		Late stage cancer	
10 years to develop	1 - 3 years to develop		60% of new cases are detected late stage	
Polyps from less than 0.5 cm to 3cm and above	Stage1	Stage 2	Stage 3	Stage 4
5 years survival: 100%	94%	82%	62%	8%

(1) Journal of National Cancer Institute, 2009

Wikipedia article on the TNM cancer staging system:

Name of study	Length	Nb of patients	Δ mortality
Minnesota (1)	18 years	46 561	-21% / -33%*
Funen, Denmark (2)	10 years	137 485	-18%
Nottingham, UK (3)	10 years	152 059	-15%

Screening frequency biennial FOBT except* annual FOBT

(1) Wineaver et al. Gastroenterology, 1997 (2) Jorgensen et al. Gut, 2002 (3) Scholefield et al. Gut, 2002

In 2010, the average annual treatment cost of a Medicare CRC patient was $140 000. If already metastised at the time of diagnosis, the average cost of treatment increases to $310 000. (source: Mariotto, Journal of National Cancer Institute, Jan 2011)

If it wasn't for Nike's copyright, CRC screening slogan could be summed up with: JUST DO IT !

Cutting through the polyp maze: lesion typing and terminology

The nomenclature describing colorectal lesions is continuously evolving, especially as new findings about signalling pathways offer a better explanation of CRC ethiology. If one wants to avoid confusion when reading the relevant literature it is important to briefly define the most common terms used to describe this pre-cancer to cancer continuum.

A *polyp* is an elevation of the *mucosa* and can be found in the oesophagus, the stomach, the small intestine but most commonly in the colon. Colorectal cancer originates from polyps in the colon or the rectum but not all polyps turn into cancer. They can be classified as benign (*hyperplastic* polyp), pre-malignant (*adenoma*) and malignant (colorectal *adenocarcinoma*). *Neoplastic* polyps include both pre-malignant and malignant lesions and indicates that cells have lost their normal differentiation. Polyps can be described as *sessile* (flat) or *pedunculated* (with a "stalk"). Adenoma are sub-classified histologically into *tubular* (with 80%-85% of total, the most common type, also refered to as *adenomatous polyp*), *tubulovillous* (10%-15%) or *villous* (5%). At a macroscopic level their surface can appear as *traditional serrated* (TSA) or *sessile serrated* (SSA). Villous indicates that the lesion has a "hairy" appearance, serrated that it has a "saw-like" appearance.
Lastly, two terms need to be introduced as they are commonly used to distinguish between high risk and low risk lesions: *high grade dysplasia* (HGD, used to be called *carcinoma in-situ*) and *low grade dysplasia* (LGD). In pathology dysplasia refers to an abnormality of development and is often indicative of an early neoplastic process.

The risk of a polyp to turn into CRC depends mainly on 3 factors: a) the degree of dysplasia, b) the type of the polyp and c) the size of the polyp.

tubular adenoma	Tubulovillous adenoma	Villous adenoma	< 1cm	1 cm	2 cm
5%	20%	40%	<1%	10%	15%

risk of cancer within 12 months

Finally it is important to know that SSA are mainly found in the right side of the colon. As they are easily mistaken for flat neoplastic lesions, they are at highest risk of being overlooked during colonoscopy. They are believed to be the most common cause of *interval CRC*, ie following a first colonoscopy. The five studies which were conducted on the subject, estimate between 3.5% and 9% their overall share of diagnosed CRCs, 2/3 of which could have been avoided. (source: Silvia Sanduleanu, Incidence and potential explanation of interval colorectal cancers, May 2012.

Wikipedia article on colorectal polyps, and details on colorectal cancer pathology

How to screen for CRC ?

The list of available CRC screening options is long: colonoscopy, flexible sigmoidoscopy, CT colonography, double contrast barium enema, stool DNA and of course FOBT (faecal occult blood test) and FIT (faecal immunological test). It is also very confusing, as not all professional associations agree on what should be the recommended screening option. The ones they all agree on, and represent the de facto standards are: colonoscopy, FOBT and FIT.

USPSTF (US Preventive Services Task Force) is the most evidence-based association. The Multisociety Task Force on Colorectal Cancer (regrouping many GI associations and the American College of Physicians) , the ACS (American Cancer Society) and the ACR (American College of Radiology), agreed on common guidelines in 2008. Details of the specific guidelines can be found on their respective homepages.

The point to remember here, is that it is confusing, even for GPs, and that declaring colonoscopy as the "preferred CRC screening strategy" is the path of least resistance for the associations and the GPs.

"What's wrong with the established CRC screening methods ? It's the compliance rate, stupid !"

Estimates of the compliance rate in the US range from 55% to 65%. They rely on phone surveys and the question asked is "have you had a screening colonoscopy in the last 9 years, OR a flexible sigmoidoscopy in the last 4 years, OR a stool-based test (FOBT or FIT) in the last 12 months ?". It is fair to say though that screening compliance has been on the rise, mainly because of the steady increase in colonoscopy, 4,3m of which were performed last year. Even this seemingly precise figure is only an approximation as it is not always possible to distinguish between a diagnostic and a screening colonoscopy because of differences in reimbursement policies. The share of FOBT/FIT screening reached a high in 2001, with the only noticeable development being the shift from FOBT to FIT. A combined 10.2m FOBT/FIT tests were performed in 2010, 34% of which were FIT vs 2% in 2004. A rule of thumb calculation goes like: 10 x 4,3m (colonoscopies) + 10.2m (FOBT+FIT) = 53,5m Americans compliant with screening recommendation. There are 80,5m Americans aged 50-75y according to the 2010 Census, ie the screening rate is 53.5/80.5=66%. The last comprehensive data was gathered by the CDC in 2000, which is about to start a new survey: Survey of endoscopic capacity SECAP II, CDC, Nov. 2012

In 2008, a national CRC screening program was introduced in France. And although it was by invitation and completely free for the eligible population, after 4 years the compliance rate was levelling off at 30%. In 2012, the FOBT test was replaced by the FIT test, and the compliance rate only edged up to 32%*. Germany is the only other country along with the US which offers colonoscopy as a free screening option starting at age 55, although without invitation. The compliance rate is about 19%. In general in Europe, the compliance rates hovers around 30%, and is estimated below 20% in Japan.

* Although anecdotal, early evidence of a possible breakthrough of EPC in France was given mid December by the head of the CRC national screening program at INCa (Institut National du Cancer), Prof. Richard Benamouzig, who was quoted in the French women's press as mentioning the blood based test as the future national screening program test. I haven't been able yet to follow up on that information, but so far I hadn't considered it even remotely possible !

EpiProColon (EPC): methylation of Septin9 as biomarker of CRC

Epigenomics (I am referring to the science, not to the company) is perhaps the hottest pocket of fundamental biology research these days. But this is fairly new. To my knowledge, "The Epigenome – Molecular Hide and Seek" by Alexander Olek (founder of ECX and first CEO) and Stephan Beck (The Sanger Center, Welcome Trust) is the first book, published in Jan 2003, and dedicated solely to the subject. This early focus on post-translational gene regulation research gave ECX a headstart in identifying the most promising cancer biomarkers based on DNA methylation. In layman's terms DNA methylation can be compared to a reversible, chemical on/off switch of expression of genes by the docking of a small methyl group to cytosine. It is depicted in ECX's corporate presentation decks. For more detailled information about DNA methylation see the Wikipedia and Nature articles.

HPV testing: the template for EPC ? Yes and No, uptake should be faster.

HPV DNA testing is the first large scale and successful MDx test, with sales around USD 500m. Some versions have been around since 1991 but it is not until 2003 when a small company, Digene, got FDA approval for screening that sales really took off. Digene was finally acquired by Qiagen in 2007 for USD 1.5 bn. By that time sales were totalling USD 180m. It is true that HPV testing took a long time to reach inflexion point, but I see several reasons for a quicker take-off by a blood-based CRC screening test.

First, PAP smear testing does a pretty good job at identifying pre-cancerous lesions (CIN). What a HPV test does is detect an HPV (Human Papillomavirus) infection in the cervix area, which in turn might lead to cancer. There are over 30 strains of HPV viruses and less than a handful are of any concern. On top of that, the infection is generally transient, ie the immune system gets rid of it on its own within a couple of weeks. Having said that it is a fact that virtually all cervical cancers are the result of an HPV infection. It took some time to scientifically establish that detecting an HPV infection had a positive impact on reducing cervical cancer mortality. EPC is different quite obviously, it doesn't detect a virus that might or might not lead to cancer, it detects the actual cancer. Basically there is a higher sense of urgency about CRC screening than about HPV screening.

Secondly, standardisation of detection and amplification methods has gone a long way. In the early days of HPV testing, PCR wasn't yet the standard amplification method it is today. The Digene/Qiagen HPV test was running on the HC2 (Hybrid Capture) technology. This a bit a bit like Betamax vs VHS. This uncertainty has been taken out of the equation. The reduced need for capital expenditure is surely to be considered a positive. (This is true of the HPV vs EPC comparison and much much more so of the EPC vs Cologuard one)

Thirdly, HPV testing is based on a smear sample from the cervix area, which has to be performed by a gynaecologist as opposed to a blood sample which can be performed by any medical support staff. Finally, the frequency of face to face meetings with a specialist as compared to the frequency of a face to face meeting with the GP is also supportive of a quicker uptake.

The FDA PMA certification: show me the data !

Let's face it, FDA regulation is tricky in general, but medical device regulation is a nightmare ! The original FDA wording is summarized in 2 sentences:
35 17 "there is reasonable assurance the device is **safe** and **effective** for its **intended use** as prescribed in the product **labelling**; and
35 17 the device manufacturing facilities, methods, and controls were inspected and found to be **in compliance with the Quality System regulation**"

- Safety: that's an easy one, one can safely say that safety is of no concern.
- Quality control: also an easy one. The IVD kits are manufactured by a cGMP supplier NextPharma. The agreement was signed late 2010 already.
- Intended use (IFU): it should read along the lines of:
"The EpiProColon CRC screening test is intended for use as an adjunctive screening test for the detection of methylated septin9 as a marker of CRC. A positive test result should be followed by colonoscopy. A negative result could refrain from any other investigation and resubmit to testing every –frequency- (yearly or every other year). The test should be used on subjects who are typical candidates for CRC screening, adults of either sex, 50 years or older, who are at average risk for CRC.".
- Labelling: it should list the exclusion criteria, like pregnancy, hereditary forms of CRC and Crohn's disease for instance. It should also underline the fact that no diatery restriction is required before taking the test, and most importantly, that no pre-existing condition requiring medication is an exclusion criteria. See page 15/103 of the October 2012 AMP presentation by Molecular Pathology Laboratory Network Inc. (unfortunately the 103 pages pdf presentation is no longer available on Epigenomics homepage, but feel free to contact me).
- Effectiveness: answers the question: how good is the test at what it is supposed to do ? The 2 basic metrics that measure the performance of a screening test are *sensitivity* and *specificity*. The former answers the question: how good is the test at identifying subjects as having a disease who actually have the disease. The latter answers the question: how good is the test at identifying subjects free from the disease who are actually free from the disease. Other metrics like *positive predictive value* (PPV) or *negative predictive value* (NPV) can be derived from them and incidence of the disease. The mathematical definitions are:

Sensitivity = TP / (TP + FN) = true positives / (true positives + false negatives)
Specificity = TN / (TN + FP) = true negatives / (true negatives + false positives)

Before getting into the details of the clinical data filed with the 4th module, it is important to give a historical perspective of the development of EPC. First it is important to remember that since the beginning, back in 2005, EPC was always about the same one thing: measuring the methylation level of the septin9 gene. 13 case control studies (4500 patients) and 1 prospective study (7940 patients) were performed since 2005. Abbott conducted its own trial for CE marking in 2008 under a global IVD licensing agreement, Quest and ARUP presented their respective LDT trials for the US market in 2010 and 2011 respectively. ARUP was the first to publish detailed data on the improved assay, which is basically the version submitted to the FDA. These trials generated a lot of data, usually summarized graphically by the company in the appendix of the corporate presentation deck. The picture is very consistent and converges to a performance level of 90% sensitivity at 85% specificity for the case control trials. The PRESEPT prospective trial (or 2 prospective trials, if one considers the US pivotal study a separate one), needs commenting, but back in January 2010, demonstrated 67% sensitivity at 88% specificity in an asymptomatic screening population.

The PRESEPT study: Murphy's law ? Or maybe not !
The PRESEPT study was hailed the largest ever prospective CRC screening study back in 2010, overseen by the highest profile, independent steering committee you could dream of, … and yet, its findings never made it to journals like the NEJM or even GUT. How come? To be precise, there was a late-breaking abstract presentation by T. Church (lead investigator, independent) at the DDW in May 2010, a poster presentation by T Roesch (investigator Germany, independent) at UEGW 2010, and a post ASCO 2010 summary publication by Muralidharan (Quest), but no peer-reviewed, high profile publication you would expect for such a trial. (summary of all scientific publications related to EPC).
What happened ? I believe a series of mishaps (1 of the 3 external labs had technical glitches and spoiled some samples), poorly designed study (ex-post sub-group analysis, switch from duplicate to triplicate during the trial), lack of leadership (the company had zero grip on the steering committee), and maybe even pushing for a hidden agenda by some of the reviewers (I am not a big fan of conspiracy theories, I simply cannot help the feeling). Whatever the reasons, the bottom line is that 30 months after completion, the PRESEPT study hasn't been published, which means it has no scientific existence! If you remember my remark about the presentation by Dr Walsh in the introduction, you surely understand my frustration.

The US pivotal study: same player shoot again? Definitively not!
The PRESEPT study was never meant to be the US pivotal trial. It was the (missed) opportunity to get the community on board, but also one big rehearsal, with a view to get the PMA trial right. It was the starting point to fine-tune the assay (the pre-analytical sensitivity was doubled from EPC v1.0 to EPC v2.0), taking on board the cumulated experience of Quest and ARUP on top of its own one. It was as importantly the opportunity to collect multiple blood samples, with a view to offer a turnkey package to the planned three global IVD licensees. Abbott was already on board, but there were two more slots to be sold. Qiagen took a 24 months option early 2011, one is still available ex Japan for which Sysmex has an option. In autumn 2011, the IVD kit v2.0 is ready, it has been extensively tested and CE marked. Time to get the frozen blood sample out of the freezer. This time the data is "clean", although the expected incremental performance improvement is left wanting. I'll come back to that in a minute. More data is needed says the FDA and requires a direct comparison with FIT. The most immediate consequence is again a delay in the much needed publication in the scientific press. No pharmaco economic study, no peer-reviewed article, nothing. But with the release of positive headline data of the FIT non inferiority study early Dec 2012, the last box has been ticked. There is an avalanche of publication to be expected in 2013! All right, enough historical wandering, let's get back to the question to be answered: is the test good enough?

ECX has been interacting with the FDA since early 2008. It was agreed then that the prospective trial would not require collecting any stool sample as colonoscopy was the only control needed. When it started recruitment for its PRESEPT study in June 2008, it was already clear what the test must achieve to get a PMA: "find the majority of CRCs in an asymptomatic screening population". The FDA wasn't more specific, neither didn't it impose a minimum specificity target, as it considers that this metrics is more relevant to payors. ECX set itself a target of 85%-89% specificity for the PRESPET study, which came out at 88%, whereas the US pivotal study read out at 80% in December 2011. This figure was clearly a disappointment and triggered the FDA to ask for additional data in the form of a non-inferiority study vs. FIT. FIT had never been assessed in a prospective trial in the US, but had been extensively scrutinised in Asia (Morikawa 2005) and increasingly used in the US. The EPC vs. FIT non inferiority study started recruiting in April 2012 and presented positive headline data in December.
The clinical package filed with the FDA includes mainly the following data: CE marking study, US prospective trial, the Molnar study (left/right detection rate, p13/37 December presentation) and the EPC vs. FIT non inferiority study.

Sept9	**US pivotal**			
design	prospective			
# screened	7929	TP	30	
# sample	1479	FN	14	
# controls FP	290	TN	1145	Spec.
date	Dec 2011			80%

# detected	CRC stage	pT1	pT2	pT3	pT4	pTx	
	Stage 1	4	3				7
	Stage 2			10			10
	Stage 3		2	5	1		8
	Stage 4		1	3		1	5
		4	6	18	1	1	30
	NED FP						

# actual	CRC stage	pT1	pT2	pT3	pT4	pTx	
	Stage 1	11	6				17
	Stage 2			12			12
	Stage 3	1	2	6	1		10
	Stage 4		1	3		1	5
		12	9	21	1	1	44

% sensitivity	CRC stage	pT1	pT2	pT3	pT4	pTx	
	Stage 1						41%
	Stage 2			SENSITIVITY			83%
	Stage 3						80%
	Stage 4						100%
		33%	67%	86%	100%	100%	68%

Sept9	**CE mark**			
Design	case control			
# screened	Na	TP	93	
# sample	373	FN	5	
# NED	149	TN	126	Spec.
Date	Sep 2011	FP	23	85%

# detected	CRC stage	pT1	pT2	pT3	pT4	pTx	
	Stage 1		24				24
	Stage 2			21	6		27
	Stage 3		1	28	2		31
	Stage 4			10	1		11
		0	25	59	9	0	93
	NED FP						23

# actual	CRC stage	pT1	pT2	pT3	pT4	pTx	
	Stage 1		27				27
	Stage 2			23	6		29
	Stage 3		1	28	2		31
	Stage 4			10	1		11
		0	28	61	9	0	98

% sensitivity	CRC stage	pT1	pT2	pT3	pT4	pTx	
	Stage 1						89%
	Stage 2			SENSITIVITY			93%
	Stage 3						100%
	Stage 4						100%
		0%	89%	97%	100%	0%	95%

EPC vs FIT	EpiProColon			
design	case control		301	
# screened	na	TP	73	
# sample	301	FN	30	
# NED prosp.	198	TN	160	Spec.
date	Dec 2012	FP	38	81%

# detected	CRC stage	pT0	pT1	pT2	pT3	pT4	pTx	unkn.	
	Stage 1	2	4	8				0	14
	Stage 2				10	2			12
	Stage 3		0		13	1			14
	Stage 4		2		0	6	1	2	11
	Stage X		1		1		6	14	22
		2	7	8	24	9	7	16	73
	NED FP								

# actual	CRC stage	pT0	pT1	pT2	pT3	pT4	pTx		
	Stage 1	3	8	11				1	23
	Stage 2				14	2			16
	Stage 3		1		18	1			20
	Stage 4		2		1	6	1	2	12
	Stage X		1		1		6	24	32
		3	12	11	34	9	7	27	103

% sensitivity	CRC stage	pT0	pT1	pT2	pT3	pT4	pTx	unkn	
	Stage 1								61%
	Stage 2								75%
	Stage 3				CRC SENSITIVITY				70%
	Stage 4								92%
	Stage X								69%
		67%	58%	73%	71%	100%	100%	59%	71%

EPC vs FIT	FIT			
design	case cont		296	
# screened	Na	TP	66	
# sample	296	FN	32	
# NED prosp.	198	TN	195	Spec.
Date	Dec 2012	FP	3	98%

# detected	Stage	pT0	pT1	pT2	pT3	pT4	pTx	unkn.	
	Stage 1	0	3	10				1	14
	Stage 2				10	2			12
	Stage 3		1		15	1			17
	Stage 4		1		0	4	1	1	7
	Stage X		1		1		2	12	16
		0	6	10	26	7	3	14	66
	NED FP								

# actual	Stage	pT0	pT1	pT2	pT3	pT4	pTx	unkn.	
	Stage 1	3	8	11				1	23
	Stage 2				14	2			16
	Stage 3		1		18	1			20
	Stage 4		1		1	6	1	2	11
	Stage X		1		1		6	20	28
		3	11	11	34	9	7	23	98

% sensitivity	Stage	pT0	pT1	pT2	pT3	pT4	pTx	Unkn.	
	Stage 1								61%
	Stage 2								75%
	Stage 3				CRC SENSITIVITY				85%
	Stage 4								64%
	Stage X								57%
		0%	55%	91%	76%	78%	43%	61%	67%

In the EPC vs. FIT study, the controls included 24 advanced adenoma (defined as HGD or adenoma with villous component or larger than 1cm) and 73 small polyps. EPC identified 3 AA and 10 polyps, whereas FIT identified 1 AA and 1 polyp.

One of the main issues with EPC data (according to analysts covering EXAS) is the seemingly high variability of performance. I believe this is not a real issue. Here is why. Screening for CRC is not

comparable to screening for any other cancer type, as colonoscopy enables to sample the full continuum between healthy tissues and CRC. Breast is based on imaging techniques, HPV detects a virus and PSA is simply poor. Considering that the distribution of histologic findings varies from one trial to the next (nb of pT1, pT2, pT3 and pT4 cases) and that sensitivity is a function of histology it is only logical that estimates of sensitivity fluctuate. This is particularly true of case control studies. Prospective studies, if large enough, and with sequential enrolment, are less prone to this phenomenon. The higher sensitivity of case control studies compared with prospective studies is explained by the fact that almost all pT1 cases are treated during the colonoscopy and therefore disqualify for recruitment in the active arm. Being deprived of pT1 lesions, ie enriched with pT2 lesions or higher, overall sensitivity is higher in case control studies.

Another bias explains the variability of specificity. The control arm is systematically enriched with cases like adenoma or polyps in order to test if there is a sensitivity for these pre-cancerous lesions. This happens both in case control and in prospective studies. As a consequence the proportion of truly asymptomatic patients can vary a lot, hence the impact on specificity.

Quest has been using its LDT version of EPC since early 2011. I estimate that about 80 000 tests have been sold to date. Quest indicated during its recent AMP presentation that the overall positivity rate has been 6,7%. If one assumes that CRC incidence is 0,7%, Quest's experience suggests that EPC has a 94% specificity. You could argue that Quest's experience is biased, and you may be right, but in any event this number is much closer to the actual specificity than 81%. Why is it so high ? I would argue that many of these 80 000 patients are "early adopters", "medical geeks" if you want: highly educated, mostly white (incidence is higher in the black population), high earner. Maybe they even test twice a year, just to make sure.

Introducing a new metrics: the "colonoscopy relevant specificity".
What do I mean by this? Let me give you an example. Let's assume EPC's CRC specificity is 90%. That implies that if I a test a cohort of 100 individuals, 10 will be CRC false positive. Let's now also assume that there is no CRC at all in the 100 cohort, but that 2 of them have an adenoma. It is desirable that the adenoma be taken out, and these 2 individuals are not genuine false positives. In this example the "adjusted", colonoscopy relevant specificity is therefore 90 / (90 + 10 – 2) = 92%.

My point is quite simple. Given the accumulated data and the range of estimates for specificity, there is nothing there that could disrupt the current utilisation pattern of endoscopic capacity because of a sudden influx from septin9 false positives. Consequently, the FDA will stick to its mandate, ie make sure that the blood test is fulfilling its purpose, ie finding as many CRCs cases as possible, ie favour sensitivity. It will leave the specificity and cost discussion to other parties.

The competition

The search for cancer specific blood based biomarkers has been very elusive so far. The shortcomings of PSA have been described above. CEA (carcinoembryonic antigen) for instance is commonly used as a recurrence biomarker only, as it completely lacks any specificity.
Research has been concentrated on methylation of specific genes, microRNA and complex host-response profiles.
MDxHealth (MXDHF PK, Belgium): MDxHealth was known as OncoMethylome until late 2010 before it took the strategic decision to stop its development effort of a CRC screening test based on the methylation of two genes. Data up to that point were only marginally behind those of ECX, but both the timeline and the cost involved of bringing the product to the market motivated the decision. NDRG4, one of the two methylation markers used by EXAS was licenced in from MDxHealth.

GeneNews (GNWSF PK, Canada): introduced its microRNA based test ColonSentry in parts of Canada in 2008. The performance in case control trials indicated sensitivity of 72% for a specificity of 70%. No prospective trial was ever done. With its hefty price tag of CAN$ 600 and poor performance, ColonSentry never recorded any significant sales.

Exiqon (EXQNF PK, Denmark): Exiqon is a technology company, supplying labs worldwide with microRNA research products. It has been recently trying to apply its knowhow to identify CRC specific microRNA biomarkers. With only very limited data so far, limited financial resources, and a delayed start for a first small European prospective trial, chances for a successful development are slim, or at least in a distant future.

Diagnoplex (private, Switzerland): Diagnoplex's solution is based on measuring the host response. It doesn't detect the presence of a tumor directly but indirectly, by measuring a 29 biomarker molecular signature. Preliminary data of a first validation study recently showed 67% sensitivity at 92% specifity.

Signature Diagnostics (private, Germany): similar concept as Diagnopex, but following RNA extraction uses an Affimetry chip for hybridization. An exploratory study measuring the expression of 202 genes was presented in 2010.and showed 90% sensitivity at 88% specificity.

You would think that the prospect of a $1bn+ market should motivate many players to try and find a blood based CRC screening test. In fact this is limited to start-ups with limited funding. Big pharma is not even paying lip service to support them. Roche Diagnostics was Epigenomics's global and exclusive partner until 2006 when Roche Group decided, following a "strategic review", to stop the collaboration. Today, none of the companies mentioned above have any cooperation agreement with any big diagnostics player, not to mention big pharma. The standard set by ECX in the search for the "silver bullet", the single, highly specific biomarker will be difficult to improve on. Multi factors or multi targets solutions increase both costs and the level of complexity, which require a vast amount of data to support the claim. This is time consuming and expensive. With a PMA under their belt, both EXAS and ECX will set the bar only higher for any other contender for years to come.

The cost effectiveness or pharmaco economics of CRC screening

Even in such different healthcare systems as the US and Canada, cost effectiveness studies show that screening for CRC not only reduces mortality but decreases costs. Let me quote the conclusions of two prominent papers that were published in 2010.
- Effect of rising chemotherapy costs on cost savings of colorectal cancer screening, Feb 2010, JNCI
"With the increase of chemotherapy costs for advanced colorectal cancer, most colorectal cancer screening strategies have become cost saving. As a consequence, screening is a desirable approach not only to reduce colorectal cancer incidence and mortality but also to control the costs of colorectal cancer treatment."
- The cost-effectiveness of screening for colorectal cancer, Sept 2010, CMAJ
"Screening of average-risk individuals for colorectal cancer is a cost-effective measure, even with less-than-perfect compliance. Recognizing that decisions about screening for colorectal cancer depend on local resources and individual patient preferences, either an annual high-sensitivity faecal test, such as a faecal immunochemical test, or colonoscopy every 10 years offer good value for money in Canada."

None of these studies include EPC. In 2011 though Dr Uri Ladabaum completed a first cost-effectiveness study. The conclusions were presented at the DDW in May 2011, but the study itself has never been published, simply because the underlying PRESEPT study (the 1st prospective performance study) has never been published ! Here are his main findings: "under optimal uptake and adherence mSEPT9 every 2 years decreased CRC incidence by 41% and mortality by 61% at cost of $8400 per quality-adjusted life years (QALY) gained vs no screening ….. The costs of colonoscopy and CRC care were the most influential variables on the cost-effectiveness of all strategies. At the population level, mSEPT9 yielded the greatest incremental benefit at acceptable costs, when it increased the fraction of the population screened, as opposed to substituting for current strategies."
So clearly in Ladabaum's base case, EPC makes perfectly sense as an additional CRC screening option. I believe further that his calculation is underestimating the attractiveness of EPC. Indeed some critical inputs are questionable: a) price/test $ 150 vs $ 100 according to information directly from Quest. b) localised CRC sensitivity 51% vs 59% in US pivotal study c) price of colonoscopy was the Medicare price and not the actual average billed price of about $1500 in real-life setting, including sedation and GP referral. (split up of colonoscopy costs).

Cost-effectiveness studies are useful tools, although something of a black box for most people like you and me. The complexity of Markov and other models hide some very structural flaws. I refer in particular to non medical costs, incurred exclusively by the patient or his employer, and invisible to the healthcare system. These are not to be mistaken with copayments, they include for example transportation cost and time off work. A study published in 2007 in the CA Cancer J Clin. estimated the non medical cost per FOBT test at $36 and $308 per colonoscopy. These costs are likely to be minimal, if measurable at all, in the case of EPC.

In order not to be left in the dark, I have tried to come up with my own, simplistic version of a cost effectiveness model. It is partly depicted below. The blue figures are freely defined inputs, the red figures are the value of these inputs in any particular year (only 2 of the 10 years of the model are shown) and the black figures are the result of calculations. Instead of considering the whole heterogeneous population of 50-75 years old, I have chosen to run my analysis on the 4,5m Americans who turn 50 every year and follow them for the next 10 years. In order to have more telling figures I further limited myself to a sample of 100 000. The bottom line is that, even taking into consideration the screening cost alone (not the reduction of cancer treatment costs), screening with EPC is cheaper that colonoscopy. In my example, $137m vs. $150m over 10 years for 100 000 screened individuals, ie $137/person/year vs $150/person/year. This model might look over-simplistic, but in fact it systematically underestimates the cost advantage of EPC vs colonoscopy. The only debatable issue is the 93% specificity, but I refer to my explanation about specificity above.

	Sample Year		Definitions	Cumulative Year 1 to 10		Year 1	Year 2
Incidence	0.60%					0.60%	0.60%
sensitivity (start/end)	71%	71%	TP/(TP+FN)			71%	71%
specificity (start/end)	93%	93%	TN/(TN+FP)			93%	93%
end perf.values after years		5					
Screening frequency	1		interval in years between screenings			1	1
# screened	100 000		# positives + # negatives	709 730		100 000	92 092
# cancers	600		incidence x # screened or TP+FN	4 258		600	553
# positives			TP+FP				
# negatives			TN+FN				
TP	426		# cancers x sensitivity	3 023		426	392
FN (missed cases)	174		# cancers – TP			174	160
FP	7 482		# cancer free x (1-spec) / spec	53 100		7 482	6 890
TN	91 918		# screened - # cancers – FP			91 918	84 650
PPV	5.39%		TP/(TP+FP) or TP/#positives			5.39%	5.39%
NPV	99.81%		TN/(TN+FN) or TN/#negatives			99.81%	99.81%
# colonoscopy	7 908		TP+FP or #positives	56 123		7 908	7 282
Unit test price	75					75	75
Unit colono. Price	1500					1500	1500
test total cost	7 500 000			53 229 759	39%	7 500 000	6 906 921
colon. total cost	11 861 581			84 185 211	61%	11 861 581	10 923 600
total screening cost	19 361 581			**137 414 971**		19 361 581	17 830 521
		vs	**100% colonosocopy in year1**	**150 000 000**			

The payor's view

We have seen above that based on a basic cost effectiveness model, all payors should support the introduction of EPC as a new CRC screening option and consequently reimburse it. This is somewhat of an oversimplification though as the regional and company specific settings vary greatly. Factors like demographics (age, ethnicity, population density) and available endoscopic capacity are relevant to understand where health organisations stand, Kaiser Permanente for example is very keen on improving the compliance rate and implementing a pre-colonoscopy triage. His former CMO Dr Jeffrey Weisz, made this point very clearly in the following video interview (4mn43s), sponsored by Polymedco, a leading FIT supplier. Furthermore, Kaiser is sponsoring a trial to find out whether there is any benefit in a sequential combination of EPC and FIT. (clinicaltrialgov trial reference NCT01574677). This trial hasn't started recruitment yet, but it is evidence of Kaiser's dual intention: to improve compliance and to limit colonoscopy to a second line screening procedure. United Health (UNH) is also an outspoken supporter of a blood based test. None of the major health organisations have issued a negative opinion, they are in a wait and see mode at worst.

One very important condition for a smooth organisational uptake has been the issuance by the AMA (American Medical Association) early 2012 of a specific CPT code including mSeptin9 tests. CPT 81401 has in the meantime been confirmed in November and will start been used in January 2013 on a $250/test basis. This shouldn't be the actual billed price considering the average $100/test currently charged by Quest for its LDT version.

Discussions with CMS have been going on in the background but needless to say, won't be finalised before at least FDA approval.

The lab's view

This is in my opinion, the crucial link in the chain. If EPC makes sense for the lab (read Quest), it will fly, if it doesn't, it won't. I have set up a little model to find out. My starting point is the end-patient price I used above: $75/test. Another key input is Quest's gross margin: 57% (if not diluting the gross margin is considered the minimum requirement from Quest's point of view). If one uses 200 as the number of tests/day/lab technician and applies the average hourly wage in the sector, the purchase price per test that balances the model is $31. That leaves me with the last question to be answered: what is ECX's profitability with a $31 selling price ? The answer as always in such cases depends on volume assumptions. Relying on indications I got from the industry, in a high volume scenario, a price as low as $5/kit is a realistic assumption. This may appear completely unrealistic today, but a few years out, and considering that this price could be squeezed out by a much bigger player, ie ECX's eventual acquirer.

I am aware that this is an oversimplification and that Quest is more likely to look at ROCE or EBIT margin to assess the business opportunity of any given product, but at least it gives me a starting point to test my scenario.

Colonoscopy: screening gold-standard or diagnostic gold standard ?

Asking the question is not going to make me popular in the gastroenterologist community. But should it stop me from asking ? I don't think so. More importantly than my personal opinion is the opinion of recognised experts. And some are beginning to ask the same questions. In a seminal November 2011 editorial of the Journal of the National Cancer Institute, Russel Harris and Linda Kinsinger chose as title: "Less is more: "Not going the distance" and Why"
The whole article is a must read ! Here is my favourite part: "The issue of overdiagnosis, a term that has primarily been used with other cancers, should be considered because overdiagnosis is also a major problem for colonoscopy screening. The great majority of findings at colonoscopy are small low-risk adenomas and non-adenomatous polyps, not cancers. Removing any polyp increases the risk of complications, yet current practice in the United States is to remove all polyps, regardless of size, which exposes patients to a higher risk for harm with minimal (if any) gain. Removing all polyps also increases the cost of screening. When our goal changes from reducing CRC mortality within reasonable levels of harms and costs to eradicating every existing polyp, we are taking our eyes off the ball, focusing on an intermediate endpoint with an uncertain net effect on the patient."

The right-sided vs. versus left-sided CRC controversy: colonoscopy is not immune, EPC is !
In a Dec 2008 article by Baxter et Al. published in the Annals of Internal Medicine and commented by Ransohof, it reveals that mortality of right-sided CRC is not lowered by colonoscopy !

The colonoscopy specific risks and drawbacks:
Let's remind ourselves of the obvious: colonoscopy is an invasive procedure. Of all methods used for cancer screening purposes (breast, cervical, colon and prostate) , it is by far the most invasive procedure. (let us not elaborate on the specifics of DRE, which has been unanimously disqualified as a reliable screening procedure).
There are the obvious risks and drawbacks which are well documented in many US and international studies: bleeding (1.5/1000), perforation (1/1000), death (1/15 000). I suggest to read the following UK study, published in GUT, as it is both big and blunt. Figures may look a little bit better in the US, as risk is correlated with the level of experience of the endoscopist, but I couldn't find any better one for my purpose. See also the Risks section of the Wikipedia article on colonoscopy. It all starts prior to the actual colonoscopy, with the bowel preparation: nausea, vomiting, allergy (rare), followed by post colonoscopy diarrhea, dehydration, kidney damage (rare). 20% of colonoscopies require bowel cleaning by the endoscopist. This is, if not a reason for missing lesions, a reason for cost overrun. As 95% of colonoscopies involve sedation, there are also all the typical sedations related risks: allergy, cardio-vascular, pulmonary, headaches. There is hardly any data on these issues, so they are easily brushed aside. I look at it from another point of view, I do not believe it is necessary to come forward with any figure to be credible, I ask the question: why should a screening procedure involve any risk, if there are riskless alternatives ?

Finally, there is overdiagnosis, bearing in mind some findings already mentioned above (only 1 in 100 adenoma turns to cancer per year and only 1 in 400 polyps turns to cancer per year), and you should agree with me that the debate is just beginning.

I do not believe it will take too many years before a performing and convenient blood based CRC screening test or a performing and cheap stool-based test (FIT) will make up the first line options of CRC screening. Colonoscopy may not be taken off the guidelines, but its use will be de facto limited to a second line, diagnostic one. If not the USPSTF, the health insurers will make it happen; if not the health insurers, the GPs will make it happen; if not the GPs, the consumers will make it happen. Somebody will make it happen.

EPC: fast forward 2015

EPC has been present in the market as a PMA, high volume and automated CRC screening test for 2 years. Guidelines inclusion is effective, nationwide coverage by private insurers and CMS is completed. Patient end-price is $75 and TV ads* run by Quest drive a rapid improvement in the CRC screening compliance rate, although colonoscopy (primary screening) and FOBT/FIT are declining in absolute terms. More data starts to emerge, especially longitudinal data (ie impact of repeated screening several years in a row), new outcome studies (mortality) are planned.

* This possibility of running TV ads, like the one for a PSA test back in 2009, is, I believe, underestimated by many, especially European investors. Conversely, I believe that the influence of gastroenterologists on the screening option choice is overestimated.

The endgame.

It is not impossible to envisage a stand-alone future for neither ECX nor EXAS, but frankly it is not the most likely scenario. As I mentioned it before, my purpose is not to depict an option tree and its many hypothetical paths. There are enough analysts out there who get paid playing these games. My purpose is to try to find out the most likely scenario, based on a mixture of hard evidence and common sense.

When looking at the respective CEOs, both have a deal-making track record. In 2007 EXAS' Conroy pulled off a trade sale of Third Wave to Hologic prior to the PMA approval of an HPV test. ECX's CEO Taapken has been a venture capitalist for most of his career before turning CFO and being involved in two mergers. No winner here.

If I consider the situation from the point of view of potential acquirers, things get easier. Would I go for yet another stool based test or for a disruptive and convenient blood-based alternative ? Would I go for a hardware intensive and complex workflow, or a single biomarker assay, fitting in any lab's routine ? If I could tick all these boxes 6 to 12 months earlier than the runner up, would I still bother to consider buying it ? ECX is obviously the most likely take over candidate. If not Abbott or Roche, the likes of Qiagen, BioMerieux, LabCorp, Siemens or Quest of course are all likely names to be on the acquirer side.

From a strategic point of view, ECX is by far the most likely acquisition target of the two. In the short term though I consider its low market cap as a real handicap for a successful take over. I do not believe that historical shareholders would be willing to part from this investment at current valuation. I definitively would not ! Considering the industry's unwillingness to jump the gun, I concede that my endgame scenario comes with a 2 to 3 years horizon. Enough time for valuation and value to align.
For now, I think I have given enough information for every interested party to make up its own valuation model. I shall stop short of elaborating on mine. My forecast is a $800m minimum EV when ECX will eventually be taken over.

With no US NASDAQ listing, no incentivised analyst coverage*, no high-profile publication to show, ECX has been a sitting duck for Exact Sciences' management aggressive rethoric. Question marks were raised privately and publicly on subjects as varied as the relevance of methylation in tumorigenesis, the outcome of the non-inferiority study vs FIT, the approvability by the FDA, the selling price, the willingness of CMS and private payors to reimburse. Not to mention the willingness to focus the debate on cancer prevention away from early detection. I wouldn't really care if market expectations were more balanced about their respective prospects. But this is far from being the case. I hope that I have shown enough evidence that the tide has turned, and that facts will speak louder than words in 2013.

* both IPO lead-managers, Morgan Stanley and DZ Bank (a German savings&loans) dropped coverage of ECX late 2007 or early 2008. During its most sensitive period of strategic repositioning, ECX remained without coverage till Dec 2010, when Equinet, an independent German broker initiated coverage, addressing, unfortunately, only a domestic, sceptic and illiterate audience.

The verdict

I think Epigenomics will win this Darwinian fight. EPC is not a perfect test, but it brings to the party all you need to revolutionize the CRC early detection market: 1) performance is good enough and at least matches the performance of FIT, the best non-invasive and FDA approved option. This will lead to PMA certification by the FDA mid 2013 and guidelines inclusion further down the road. 2) its ease of use will boost compliance to levels not achievable by any stool-based or invasive alternatives. Even GPs will actively support it because it minimises the time spent trying to convince patients to take a test in the first place. 3) its economics are attractive to all parties, most critically to the labs. 4) all payors, private and CMS, will eventually support it, as the body of pharmaco-economics evidence grows.

I started with a quote, let me finish with another one from a fellow Frenchman, Victor Hugo:
“one cannot resist an idea whose time has come”.

Gilbert Gerber
January 2013