

Validation of a Nu.Q™ colorectal cancer screening triage test to identify fit positive individuals at low risk for colorectal cancer



M. Herzog¹, M. Eccleston¹, D. Pamart¹, B. Cuvelier¹, E. Josseaux¹, Hans J. Nielsen², J. Micallef¹, J. Terrell

1. Belgian Volition SPRL, 22 Rue Phocas Lejeune, Parc Scientifique Crealys, 5032 Isnes, Belgium. 2. Department of Surgical Gastroenterology, Hvidovre Hospital, University of Copenhagen, Denmark. Corresponding authors: M. Herzog, Lead Scientist m.herzog@volitionrx.com, Jake Micallef, CSO, j.micallef@volitionrx.com

Background

The success of stool based screening for CRC adopted across Europe has placed significant strain on colonoscopy capacity.

Immunohistochemistry studies show genome-wide epigenetic changes in the chromatin of cancer tissue and have identified histone-oncoproteins - histone modifications and other epigenetic changes linked to cancer. Nucleosome bound DNA fragments contain mutations found in cancer tissue suggesting a tumor chromatin origin for, at least some, circulating nucleosomes. Profiling global levels of epigenetic alterations in circulating nucleosomes can provide disease specific diagnostic information.

The aim of the study was to validate an algorithm combining Nu.Q™ blood score with numeric FIT score to triage positive Fecal Immune Tests in an average risk population i.e. identify individuals with low risk adenomas or no findings on colonoscopy.

Methods

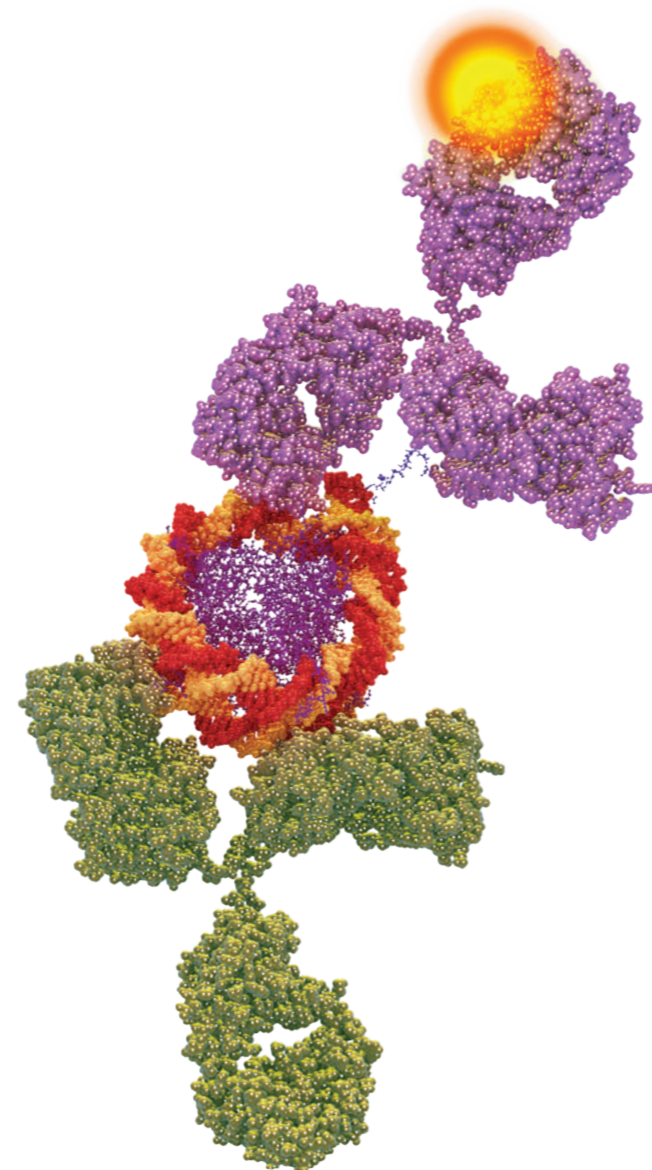
In collaboration with the Hvidovre Hospital, University of Copenhagen, serum samples were collected from FIT positive individuals with colonoscopic confirmation of diagnosis. The samples were divided into a training set (n=1907) and validation set (n=1961). 10µl serum samples from the training set were analyzed using Nu.Q™ ELISA blood tests and various algorithm developed by Linear Discriminant Analysis (LDA) to identify individuals with no evidence of cancer.

An optimal algorithm, achieving a 25% reduction in colonoscopy, was validated in an independent cohort and the performance criteria, reduction in colonoscopies and percentage of missed cancers, calculated and compared to equivalent reduction in overall colonoscopy achieved by increasing the FIT cut off scores.

Volition Nu.Q™ ELISA

Volition has developed five patent-protected families of Nu.Q™ sandwich ELISA assays, each of which captures intact nucleosomes and labels (identifies) a specific structural feature:

- Nu.Q™ - V histone variants
- Nu.Q™ - M histone modifications
- Nu.Q™ - X specific DNA modifications
- Nu.Q™ - A nucleosome-protein adducts
- Nu.Q™ - T total nucleosomes

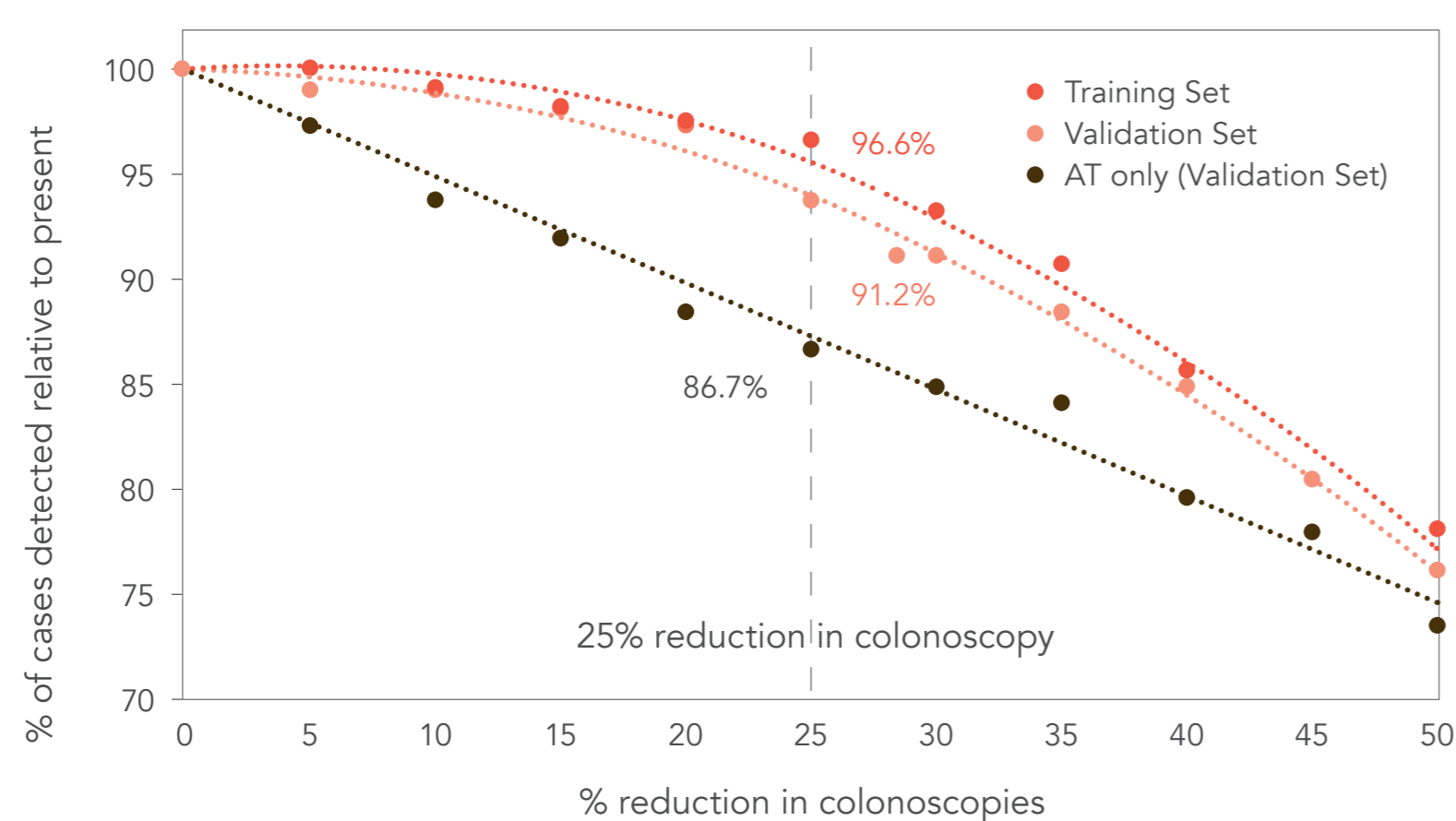


Study Demographic

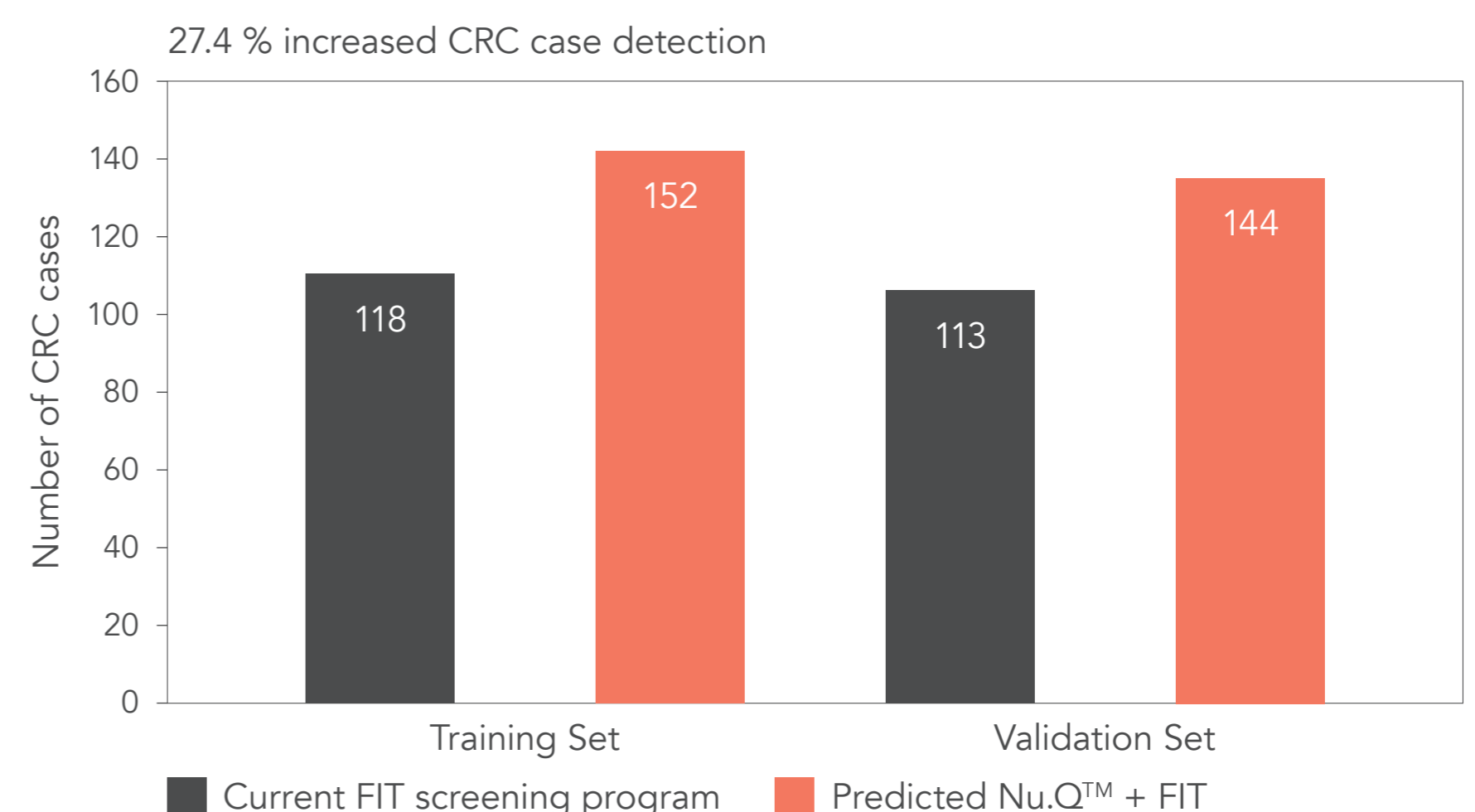
The study comprised a training set (n =1907 , T) and a validation set (n = 1961, V) aged 50 to 75 years with average risk and no prior colonoscopy who tested FIT positive for in Danish colorectal cancer screening program. Patients were classified into 3 groups by colonoscopy result.

Diagnosis	Patients		Mean Age		Male:Female	
	T	V	T	V	T	V
CRC	118	113	67.3	67.0	68:50	71:42
Stage I-II	72	76	67.4	66.7	40:32	47:29
Stage III-IV	46	31	67.2	67.3	28:18	19:12
Stage Unknown		6		69.1		5:1
Adenoma	989	1012	64.9	64.7	298:691	669:343
High Risk Adenoma	252	286	66.3	65.9	173:79	198:88
Other Adenoma	737	726	64.4	64.2	518:219	471:255
Clean Bowel	800	836	62.2	62.3	406:394	428:408
Total	1907	1961	63.9	63.8	1165:742	1168:793

Reduction in Colonoscopies vs. Nu.Q™ Triage Test Sensitivity



Potential Increase in Programme Sensitivity



Results

A single, age adjusted, Nu.Q™ blood test combined with FIT was developed to reduce non screen-relevant colonoscopies using a training set of 1907 FIT positive individuals from an average risk cohort. An algorithm was fixed at a nominal 25% reduction in colonoscopy with minimal reduction in cancer detection. The algorithm was validated in 1961 distinct FIT positive individuals from the same average risk population achieving 28.6% reduction in colonoscopies albeit with a slight reduction in sensitivity (91.2 % cancer sensitivity compared to 96.6% in the training set). The approach demonstrated significant improvement in overall cancer detection compared to adjusted FIT score (86.7%).

Conclusions

The Nu.Q™ Colorectal Cancer Screening Triage test could reduce unnecessary colonoscopies and ease pressure on colonoscopy capacity or, alternatively, detect more cancers by increasing the throughput of screened subjects.