

## Research Article

# Predicting Outcome in Colonoscopic High-Risk Surveillance

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Received: October 22, 2014; Accepted: March 03, 2015; Published: March 09, 2015

## Abstract

**Objective:** Surveillance with colonoscopy in risk groups for colorectal cancer needs to be based on adequate selection of individuals to examine and a well-devised timing. To stratify the risk of finding neoplasia at colonoscopy a cohort with increased familial risk of colorectal cancer was studied.

**Design:** Based on family history, 1203 individuals with an at least twofold increased risk of colorectal cancer were offered regular colonoscopies. The impact of different variables in the family history was assessed by logistic regression for the prevalence of adenomas and advanced adenomas. Findings at the first colonoscopy were assessed regarding the association with risk of future lesions.

**Results:** The prevalence of advanced lesions, when controlling for age, was associated with the number of first-degree relatives with colorectal cancer, with an age below 50 in the youngest family-member with colorectal cancer, but not with gender. Family history had a low impact on the prevalence of simple adenomas. The risk of future advanced lesions was only associated with the prevalence of advanced lesions at the screening colonoscopy, whereas a finding of subsequent adenomas was associated with advanced lesions, adenomas and hyperplastic polyps.

**Conclusion:** Adenomas and advanced lesions were not associated with the same risk factors. In this study the most important risk factors for advanced lesions, including cancer, were the number of first-degree relatives and a young family member with colorectal cancer. Findings of simple adenomas and hyperplastic polyps did not seem to be associated with subsequent advanced lesions.

**Keywords:** Colorectal cancer; Family history; Colonoscopy; Surveillance; Risk stratification

## Abbreviations

Ad: Adenomas; AAd: Advanced Adenomas; CRC: Colo Rectal Cancer; HP: Hyper Plastic Polyps; FDR: First-Degree Relatives; SDR: Second-Degree Relatives; TDR: Third-Degree Relatives; MMR: Mismatch-Repair; OR: Odds Ratio; CI: Confidence Interval; N: Number

## Introduction

Colorectal Cancer (CRC) is the third most common cancer worldwide and often a lethal disease [1]. Approximately 25% of all CRC cases occur in individuals with a family history of CRC. A monogenic disorder causing the disease is diagnosed in less than 5% of the cases [2]; the most common are Lynch Syndrome (LS), caused by a mutation in one of the Mismatch-Repair Genes (MMR), and Familial Adenomatous Polyposis (FAP), caused by an APC-gene mutation. Besides having an inherited high-risk mutation, the most important risk factors for CRC are number of First-Degree Relatives (FDR) with CRC and increasing age. Depending on the number of FDR, the relative risk is increased two- to eightfold compare with those without family history [3,4]. In the majority of cases, CRCs arise from adenomas in the adenoma-carcinoma-sequence [5]. Progression from normal colonic mucosa to invasive carcinoma was usually suggested to occur over a period of 4–10 years [6], except in

LS where the progression is observed to be faster [7]. Colonoscopic prevention of CRC is feasible by removal of premalignant lesions, adenomas, which has been shown to reduce both incidence and mortality in CRC [8]. Thus, colonoscopy surveillance is recommended in moderate risk groups for CRC [9]. On the other hand, colonoscopy is costly and scarce, and therefore it is important to select individuals suitable for prevention and to have a well-selected timing, regarding both surveillance interval and age at initiation of surveillance. In moderate risk groups, based on different factors in the family history, it would be profitable to identify subgroups that have the highest risk and assign priority of the colonoscopy resources to these.

Besides age and sex, parameters that can be assessed for impact on risk of CRC are the number of First-Degree Relatives (FDR), Second-Degree Relatives (SDR) and Third-Degree Relatives (TDR) with CRC [4,10,11], the kind of FDR relationship (sibling or parent) [3,4], and the age of the youngest affected individual in the family [12]. Development of colorectal adenomas is an important precursor to the subsequent development of CRC, and therefore adenomas could serve as a marker for subsequent CRC [10,13]. Thus, the detection of polyps – regarding multiplicity and adenoma advancement – has been suggested to have an impact on detection of additional lesions during surveillance [14].

We have analyzed the outcome of a 20-years colonoscopy surveillance programme to test predictors of future adenomas and advanced lesions. Based on family history of CRC, 1203 individuals with at least twofold increased risk of CRC were included. Factors taken into account were age; sex; number of FDR, SDR and TDR (cousins) with CRC; kind of FDR (sibling or parent/child); and age of the youngest affected individual in the family.

## Methods

### Patients

Since 1990, individuals with an at least twofold increased relative risk of CRC were offered a programme with genetic counselling and surveillance at the Department of Clinical Genetics at the Karolinska University Hospital in Stockholm, Sweden [15]. Data for this study were collected until June 2010. Individuals were included if they had two or more FDR, SDR or cousins (TDR) with CRC, or if they had one FDR with CRC below the age of 50. FAP and LS was excluded according to the current clinical protocol, using family history of CRC or polyposis, microsatellite instability, BRAF-mutation, immunohistochemistry on tumours or MMR gene screening [16]. All individuals were offered screening with an ileocolonoscopy every third year. Patients who had cancer before they entered the surveillance programme were not included in the study. All data were anonymized. The study was approved by the Stockholm regional ethical committee (KI 241/02; 2005/566 - 31/1).

### Study protocol

The majority of the colonoscopies were performed in a single centre at Karolinska University Hospital, and the remaining endoscopies were performed elsewhere but reported to the study centre. A standard routine video endoscope was used. The quality of the colonoscopy procedure concerning complete colonoscopies, bowel cleansing and pain control and adenoma detection rate was consistent with European guidelines for quality control of CRC screening [17]. For all polyps' localization, size and appearance was recorded and all polyps were removed and sent for histological diagnosis. In the vast majority of cases, polyps were removed endoscopically: snared, taken by cold biopsy or coagulated. The size of the polyp was estimated with the use of open-biopsy forceps. Lesions in or proximal to the splenic flexure were assigned as right-sided and those distal to the flexure as left-sided. The adenomas were classified according to the WHO-classification as tubular, tubulo-villous, villous, or serrated adenomas. The dysplasia was graded as High-Grade (HGD) or Low-Grade (LGD). An advanced lesion was defined as either a cancer, or an adenoma with an estimated diameter >10mm, a villous component larger than 20% or high-grade dysplasia. The surveillance period was defined as the time from the first colonoscopy to the last colonoscopy.

A thorough pedigree of each family was constructed, where all FDR, SDR and cousins (TDR) with CRC, as well as the youngest affected individual, were recorded. For FDRs with CRC, it was recorded whether they were siblings or children/parents. By utilizing the curves, constructed by Butterworth et al. [3] of the cumulative absolute risk of developing CRC over 20 years the absolute risk was estimated, taken into account the age of the individual and the number of FDR with CRC. Low age (<50 years) of the index-person was not considered for the absolute risk assessment in this study.

## Statistical Methods

Analyses were undertaken using the statistical software programme Statistical (version 10.0), Stat Soft Inc. ©, Tulsa, Oklahoma, USA. A  $p$ -value of <0.05 was considered to be statistically significant. Logistic regression with the modelled probability of having an advanced lesion or an adenoma during screening or surveillance was used to determine the impact of different risk factors. Age of the individual, age of the youngest in the pedigree, age of the youngest FDR, sex, number of FDR, SDR and TDR, and the kind of FDR relationship (sibling or parent), were considered. When assessing inheritance only individuals with either parents or siblings, not both, with CRC were analysed. Age at the first lesion (adenoma or advanced lesion) or, when no lesion was detected, the age at the last colonoscopy was employed in the logistic regression analyses.

Multicollinearity and interaction were considered when fitting the models, and this was the reason why a Cox-regression model was not employed. The number of FDR and the sum of the numbers of SDR and TDR were not independent covariates, and therefore two separate models were employed. In validating the multivariate fitted model, the HosmerLemeshow "goodness-of-fit" statistic (HL) was employed. A large  $p$ -value (>0.05) indicated that the null hypothesis (lack of fit) could not be rejected, meaning we do not have reason to believe that the model fitted the data on a non-acceptable level. The Student's  $t$  test employed for comparing ages in different subgroups. Incidence of adenomas and advanced lesions at surveillance were analysed by  $\chi^2$ -test, and for the multivariate analysis, a logistic regression model was employed considering age, sex, time in study and prevalence of Hyperplastic Polyps (HP), adenomas and advanced lesions at screening. The estimated number of screening cancers in the cohort was calculated by adding the expected number for each age group extracted from the age and gender specific incidence in the Swedish population [18].

## Results

### Descriptive data

The study covered 20 years of colonoscopy examinations (January 1990 to June 2010). There were 1203 individuals, 470 (39%) men, from 521 families included in the study. There were 676 (56%) individuals with one FDR, 299 (25%) with two or more FDR and 228 (19%) with only SDR and TDR with CRC. Five hundred seventy one (47%) individuals had a FDR with CRC below age 50. In the total population, the mean age at the first colonoscopy was 51.9 (range 17-86; SD 11.8) years, and for men it was 51.1 (range 21-86; SD 12.1) years, and for women 52.3 (range 17-84; SD 11.3). In total, 2293 colonoscopies were performed, and 594 (49.4%) individuals had two or more examinations performed. A relatively large cohort was recruited by the end of the study, and therefore 50.6% had only one colonoscopy examination performed. The mean follow-up time for those who participated in surveillance was 55 (SD 32) months.

### Colonoscopy findings

There were five individuals (0.4%) with six cancers; four were detected at the screening colonoscopy and two during surveillance. The expected number of screening-cancers in the Swedish population matched for age and gender (18) was calculated to be 0.8 compared to four that were found ( $p<0.001$ ).

**Table 1:** Univariate and bivariate (controlling for age) logistic regression analysis of family history variables associated with having simple adenoma or advanced lesion (n=1203).

Simple adenoma		Univariate analysis			Controlling for age		
Variable	Level of effect	OR	95% CI	p-value	OR	95% CI	p-value
Sex	Men (n=470)	1.08	0.94-1.22	0.58	1.10	0.96-1.24	0.50
	Women (n=733)	1.00			1.00		
Horizontal/vertical <sup>1</sup>	Siblings (n=207)	0.98	0.83-1.21	0.44	0.86	0.73-1.04	0.46
	Parent/child (n=568)	1.00			1.00		
Age youngest in family	<50 years (n=383)	0.85	0.63-1.14	0.29	0.92	0.80-1.06	0.57
	>50 years (n=820)	1.00			1.00		
N FDR		1.18	0.99-1.41	0.06	1.11	0.92-1.34	0.28
N SDR		1.09	0.97-1.21	0.17	1.11	0.98-1.26	0.09
N TDR		1.08	0.94-1.23	0.29	1.12	0.96-1.30	0.15
N SDR+TDR		1.08	0.99-1.17	0.10	1.10	1.01-1.19	0.03
Age of individual <sup>2</sup>		1.01	1.00-1.02	0.03			
Advanced adenoma		Univariate analysis			Controlling for age		
Variable	Level of effect	OR	95% CI	p-value	OR	95% CI	p-value
Sex	Men (n=470)	1.21	0.80-1.84	0.37	1.28	1.07-1.49	0.26
	Women (n=733)	1.00			1.00		
Horizontal/vertical <sup>1</sup>	Siblings (n=207)	2.10	1.25-3.53	0.004	1.40	0.80-2.47	0.24
	Parent/child (n=568)	1.00			1.00		
Age youngest in family	<50 years (n=383)	1.23	0.97-1.68	0.35	1.62	1.19-2.53	0.04
	>50 years (n=820)	1.00			1.00		
N FDR		1.75	1.50-2.00	<0.0001	1.38	1.10-1.66	0.03
N SDR		0.79	0.63-0.98	0.04	0.85	0.63-1.07	0.16
N TDR		0.87	0.60-1.14	0.32	0.97	0.71-1.23	0.80
N SDR+TDR		0.84	0.68-1.00	0.04	0.91	0.75-1.07	0.26
Age of individual <sup>2</sup>		1.05	1.03-1.07	<0.0001			

<sup>1</sup>Only those with horizontal (siblings) or vertical (parent/child) inheritance were included (n=775).

<sup>2</sup>Age when finding of simple adenoma or advanced adenoma, else age at the last colonoscopy.

At least one simple adenoma was found in 228 (19%) of the individuals and 94 (8%) had at least one advanced adenoma or cancer as the most advanced lesion. HP was encountered as the most advanced lesion in 208 (17%) persons. In 672 (56%) of the individuals no polyps were recorded.

### Risk factors in family history

Table 1 shows data for univariate and bivariate (controlling for age) analyses, and Table 2 shows the multivariate logistic regression analysis for the outcome of having adenomas and advanced lesions during screening or surveillance. Increased age was the strongest risk factor for both adenomas and advanced lesions. A difference was that the risk of adenomas was weakly associated with the sum of SDR and of TDR, while the risk of advanced lesions was associated with the number of FDR. There was also an association with early age at onset in the family (<50 years) with having advanced lesions but not with having adenomas. There was no difference between men and women regarding the risk of adenomas or advanced lesions. Likewise, there was no difference in the risk related to the kind of FDR relationship, except in the univariate analysis for advanced lesions where a strong association for siblings was seen, although this association could not

be observed when controlling for age in the bivariate analysis.

The absolute risk of developing cancer over 20 years, as estimated from Butterworth [3], correlated significantly both to having a simple adenoma (OR 1.09,  $p=0.0005$ ) and to having an advanced lesion (OR 1.24,  $p<0.0001$ ). Because this absolute risk was based both on age and on the number of FDR with CRC, it was not, because of Multicollinearity, possible to introduce as a variable in a multivariate analysis.

### Findings at screening colonoscopy as risk factors

Tables 3 and 4 summarizes the univariate and multivariate analyses regarding association between colonoscopy findings at screening and findings during surveillance. The univariate analysis revealed that prevalence of HP and adenomas as well as advanced lesions at screening were associated with findings of adenomas during surveillance. On the other hand, only advanced lesion at screening was associated with a higher incidence of advanced adenomas during surveillance. These results were reaffirmed in the multivariate analysis, where in case of advanced lesion, time in study, and increasing age, were associated with increased risk of these.

**Table 2:** Multivariate logistic regression analysis of family history variables associated with having a simple adenoma or an advanced lesion (n=1203).

		Model 1	#		Model 2	##	
<b>Simple adenoma</b>							
Variable	Level of effect	OR	95% CI	p-value	OR	95% CI	p-value
Sex	Man vs woman	1.10	0.84-1.45	0.50	1.07	0.81-1.42	0.62
Age of individual <sup>1</sup>		1.01	1.00-1.02	0.16	1.02	1.00-1.03	0.01
Age youngest <50	Yes vs no	0.90	0.66-1.22	0.49	0.91	0.70-1.23	0.53
N FDR		1.12	0.93-1.36	0.16			
N SDR+TDR					1.10	1.01-1.21	0.04
<b>Advanced lesion</b>							
		###			####		
Variable	Level of effect	OR	95% CI	p-value	OR	95% CI	p-value
Sex	Man vs woman	1.28	0.83-1.96	0.26	1.26	0.82-1.94	0.29
Age of individual <sup>1</sup>		1.04	1.02-1.06	0.0001	1.05	1.03-1.07	<0.0001
Age youngest <50	Yes vs no	1.53	0.97-2.42	0.07	1.7	1.00-2.47	0.05
N FDR		1.34	1.01-1.77	0.04			
N SDR+TDR					0.91	0.76-1.07	0.24

<sup>1</sup>Age when finding of simple adenoma or advanced adenoma, else age at last colonoscopy HosmerLemeshow goodness-of-fit statistic (HL): #p= 0.30; ##p= 0.34; ###p= 0.60; ####p=0.90.

**Table 3:** Correlation of colonoscopy-findings at screening and during follow-up(n=594) Univariate analysis with respect to adenoma incidence during follow-up.

Variable	N	N with Ad (%)	χ <sup>2</sup>	p-value
<b>HP at screening</b>				
Yes	174	53 (30.5)	11.06	0.0008
No	420	76 (18.1)		
<b>Adenoma at screening</b>				
Yes	149	63 (42.3)	49.48	<0.0001
No	445	66 (14.8)		
<b>Advanced lesion at screening</b>				
Yes	55	20 (36.4)	7.65	0.006
No	539	109 (20.2)		
<b>Univariate analysis with respect to advanced lesion incidence during follow-up</b>				
Variable	N	N with Aad (%)	χ <sup>2</sup>	p-value
<b>HP at screening</b>				
Yes	174	11 (6.3)	0.29	0.86
No	420	25 (6.0)		
<b>Adenoma at screening</b>				
Yes	149	12 (8.1)	1.38	0.24
No	445	24 (5.4)		
<b>Advanced lesion at screening</b>				
Yes	55	11 (20.0)	20.68	<0.0001
No	539	25 (4.6)		

N number of individuals; χ<sup>2</sup> Chi-2

## Discussion

Surveillance by colonoscopy is commonly recommended for individuals with increased risk of CRC due to family history, but recommendations for the interval between the exams and the age at initiation of screening are not unanimous. Our key issue was whether some of the known risk factors were more powerful than others in predicting risk of developing CRC during surveillance. Therefore,

1203 individuals with family history of CRC, who participated in a colonoscopy prevention programme, were studied regarding family history and the role of findings at the screening colonoscopy and of subsequent findings during surveillance. Due to the circumstance that very few cancers were detected, the prevalence of advanced lesions was used instead of CRC as endpoint when assessing the risks for CRC.



**Table 4:** Multivariate logistic regression analysis of status at screening colonoscopy associated with having a simple adenoma or an advanced lesion during follow-up (n=594). HL Hosmer Lemeshow goodness-of-fit statistic # HL  $p=0.99$ ; ## HL  $p=0.32$ .

<b>Simple adenoma</b>		<b>#</b>		
<b>Variable</b>	<b>Level of effect</b>	<b>OR</b>	<b>95% CI</b>	<b>p-value</b>
Sex	Man vs woman	1.25	0.80-1.96	0.32
Age		1.02	1.00-1.04	0.08
Time in study (years)		1.19	1.11-1.29	<0.0001
HP Yes/No		1.64	1.05-2.58	0.03
Ad Yes/No		4.29	2.73-6.73	<0.0001
AAd Yes/No		2.74	1.41-5.35	0.003
<b>Advanced adenoma</b>		<b>##</b>		
<b>Variable</b>	<b>Level of effect</b>	<b>OR</b>	<b>95% CI</b>	<b>p-value</b>
Sex	Man vs woman	0.91	0.44-1.89	0.80
Age		1.05	1.02-1.09	0.004
Time in study (years)		1.16	1.04-1.29	0.009
HP Yes/No		0.89	0.41-1.92	0.76
Ad Yes/No		1.25	0.59-2.67	0.56
AAd Yes/No		5.22	2.30-11.84	<0.0001

Our results regarding age were in line with other studies. Increased age is a well-recognised risk factor for CRC and adenomas in the context of sporadic cases, as well as in cases with family history of CRC [19,20].

One important aim was to explore whether having more distant relatives than FDR with CRC had an impact on the prevalence of adenomas and advanced lesions. We noticed that the risk of advanced lesion was increased with the number of FDR with CRC in univariate as well as multivariate analysis (OR=1.3,  $p=0.04$ ). This phenomenon was not noted for adenomas, but on the other hand, the sum of SDR and TDR seemed to have a weak influence on the prevalence of adenomas but not on advanced lesions. Our results were in line with a recent study which did not find a direct relationship between number or closeness of affected relatives and frequency of adenomas [21]. But on the other hand, as shown in a meta-analysis by Wilschut [22], for the risk of developing adenomas the existence of family history (defined as at least one FDR with CRC) seemed to be more important than the exact number of FDR with CRC. In our study, only 25% of the individuals had more than one FDR with CRC, so for the most part we evaluated the effect of having one FDR compared to having no FDR with CRC. Furthermore, in a large population-based study by Taylor et al. [23] it was stressed that family history per se, without respect to age, is not a strong predictor of exactly which individuals will acquire CRC in the next 20 years. Interestingly, the estimates by Butterworth [3] of the absolute risks of CRC – based on number of FDR and age - correlated very well both with prevalence of advanced lesions and adenomas in our study. Altogether, this might support the notion that the bivariate odds-ratios, correcting for age, could be a fair estimation of the risk contribution of each individual variable, since the bivariate odds-ratios do not differ substantially from the multivariate (Table 1 and Table 2).

Furthermore, Taylor noted when exploring different constellations of FDR, SDR and TDR, that a sole positive SDR family history was

associated with increased risk of CRC, but this risk was smaller than that of having a positive FDR family history. Our results indicate that history of SDR and TDR only contribute to a weakly increased risk of adenomas and hardly to any risk increase for advanced lesions, but we have, on the other hand, not explored different constellations of affected FDR, SDR and TDR, mainly due to limitations in the size of our study.

Having a family member afflicted by CRC before the age of 50 was of importance for the risk of developing advanced lesions but not of developing adenomas. If equating advanced lesions and CRC, our results were in line with Butterworth [3]. Taylor has also reported an increased risk of CRC if there was an FDR below the age of 50 but also when there was an SDR with early onset of CRC [11]. In fact, we have included FDR, SDR as well as TDR with CRC below the age of 50 in our analysis, and having a relative with CRC at early age increased the risk of advanced lesions.

The observation that the risk of having adenomas did not depend on CRC at early age in the family could suggest that even if adenomas are precursors of advanced adenomas – most will never develop into cancer and thus the risk of CRC does not depend much on the findings of small adenomas [24].

In the present study, the risk of advanced adenomas was higher for siblings compared to children/parents of the affected relative in the univariate analysis, but when adjusting for age the difference in risk could not be observed. Our results after adjusting for age were in contrast to many studies, which have observed that siblings of affected individuals have higher risk than parents [3,4,25] though Boardman et al. [25] studied relatives of probands with colorectal cancer below the age of 50. A higher risk in siblings might indicate an autosomal recessive inheritance pattern. On the other hand, our results were in line with other studies, one for adenomas [10] and one for cancer [11]. This might be interpreted as reflecting aging of the family members accompanied with more siblings being afflicted by CRC, rather than a true correlation. Moreover, in the univariate analysis in an Italian study, an increased risk of colorectal neoplasia that was observed in siblings compared to offspring, but was not observed in the multivariate analysis [26].

In contrast to most studies, we did not observe a gender difference regarding the risk of adenomas or advanced adenomas in our study [27], though a Japanese study reported the same observation as ours [27]. The absence of gender difference might partly be explained by that in most endoscopies dyeing with indigo carmine was employed, facilitating a higher a higher detection rate of flat adenomas in the right colon of women. However, it may also be possible that environmental factors (e.g. hormones) could play a more important role in the sporadic cases than in the familial cases.

This study also addressed risks associated with the findings at the screening colonoscopy and with the findings at the surveillance colonoscopies. A correlation between prevalence of HP and adenomas has been observed in previous studies [28,29]. In this study, HP at the screening colonoscopy seemed to correlate with simple adenomas but not with advanced lesions at surveillance. The lack of correlation between advanced lesions and HP might indicate that HP is not a marker for risk of development of CRC. Simple adenomas at the

first colonoscopy correlated with adenomas but not with advanced lesions during surveillance in the univariate analysis as well as in the multivariate analysis. Indeed, Lieberman concluded that one or two small tubular adenomas at the baseline colonoscopy represented a low-risk group and multiple or advanced adenomas represented a high-risk group for advanced neoplasia at follow-up [30]. Lieberman also suggested that there is a strong association between results of baseline screening colonoscopy and rate of serious incident lesions during 5.5 years of surveillance.

One of the drawbacks with the study was that only half of the population participated in surveillance and that the follow-up time among these was relatively short, in average 55 months. A reason for this was that a relatively large cohort was recruited by the end of the study.

In summary, our data indicate that influence of different risk factors on the prevalence of adenomas and of advanced lesions diverge, possibly reflecting that simple adenomas and advanced adenomas constitute different biological entities. Focusing on advanced lesions, this study indicated that high age of the patient, high prevalence of FDR with CRC, having a close relative with CRC below age 50 and findings of advanced lesions at the screening colonoscopy were risk factors of importance for subsequent advanced lesions during follow-up. Findings of simple adenomas and hyperplastic polyps did not seem to predict for subsequent advanced lesions. These results may have implications when designing colonoscopy surveillance programmes for individuals with family history of CRC.

## Acknowledgement

The authors are grateful to Norma Lundberg for excellent administration throughout the study and to all patients for their participation. The authors are also grateful to Goran Björck for linguistic revision.

## Funding

Financial support was provided through the regional agreement on medical training and clinical research (ALF) between Stockholm County Council and Karolinska Institutet, the Nilsson-Ehle Foundation (The Royal Physiographic Society in Lund) and the Swedish Cancer Society.

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