

Next generation sequencing panels for the evaluation of colorectal cancer and polyposis  
syndromes: a cost-effectiveness analysis

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**Abstract**

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**Background:** Next generation sequencing (NGS) panels are used frequently for the evaluation of colorectal cancer and polyposis (CRCP) syndromes in specialized cancer genetics clinics. We evaluated the cost-effectiveness of NGS panels as a first diagnostic step in the evaluation of these patients, and of adding groups of genes to these panels based their mode of inheritance and penetrance of colorectal cancer.

**Methods:** We developed a decision model to estimate the cost-effectiveness of NGS panel testing in this population, and calculated the costs and health benefits of identifying relatives with the mutation in order to prevent colorectal cancer mortality through early surveillance colonoscopy. Using primary data to estimate allelic frequencies, we classified the CRCP syndromes in four groups, according to the mode of inheritance and the penetrance of colorectal cancer. We obtained incremental cost-

effectiveness ratios to compare NGS panels to guidelines and pairs of panels according to the groups of genes tested. One-way sensitivity analysis was conducted.

**Results:** When compared to standard of care, using NGS panels to evaluate CRC in the genetics clinic resulted in an incremental cost effectiveness ratio between \$40,000 and \$66,000 per QALY. Testing only Lynch syndrome genes to the panel was not cost-effective ( $\geq$ \$124,000 per QALY), but when adding genes associated with autosomal dominant conditions with high penetrance of colorectal cancer, the test was cost effective ( $\leq$ \$69,000 per QALY). The addition of autosomal recessive genes represented less benefits but was very cost effective ( $\leq$ \$15,000 per QALY), and even the addition of autosomal dominant variants with low penetrance represented a good investment ( $\leq$ \$86,000 per QALY). Sensitivity analysis didn't change the conclusions.

**Conclusion:** NGS panels are cost-effective in the evaluation of CRC in the medical genetics clinic, and most of this cost-effectiveness is driven by the identification of variants in genes associated with autosomal dominant, highly penetrant conditions.

**TITLE**

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## ABSTRACT

**Background:** Next generation sequencing (NGS) panels are used frequently for the evaluation of colorectal cancer and polyposis (CRCP) syndromes in specialized cancer genetics clinics. We evaluated the cost-effectiveness of NGS panels as a first diagnostic step in the evaluation of these patients, and of adding groups of genes to these panels based their mode of inheritance and penetrance of colorectal cancer.

**Methods:** We developed a decision model to estimate the cost-effectiveness of NGS panel testing in this population, and calculated the costs and health benefits of identifying relatives with the mutation in order to prevent colorectal cancer mortality through early surveillance colonoscopy. Using primary data to estimate allelic frequencies, we classified the CRCP syndromes in four groups, according to the mode of inheritance and the penetrance of colorectal cancer. We obtained incremental cost-effectiveness ratios to compare NGS panels to guidelines and pairs of panels according to the groups of genes tested. One-way sensitivity analysis was conducted.

**Results:** When compared to standard of care, using NGS panels to evaluate CRCP in the genetics clinic resulted in an incremental cost effectiveness ratio between \$40,000 and \$66,000 per QALY. Testing only Lynch syndrome genes to the panel was not cost-effective ( $\geq$ \$124,000 per QALY), but when adding genes associated with autosomal dominant conditions with high penetrance of colorectal cancer, the test was cost effective ( $\leq$ \$69,000 per QALY). The addition of autosomal recessive genes represented less benefits but was very cost effective ( $\leq$ \$15,000 per QALY), and even the addition of autosomal dominant variants with low penetrance represented a good investment ( $\leq$ \$86,000 per QALY). Sensitivity analysis didn't change the conclusions.

**Conclusion:** NGS panels are cost-effective in the evaluation of CRCP in the medical genetics clinic, and most of this cost-effectiveness is driven by the identification of variants in genes associated with autosomal dominant, highly penetrant conditions.

**Keywords:**

Next generation sequencing, cost-effectiveness analysis, cancer genetics, colon cancer, gene panel

**Abbreviations:**

Colorectal cancer and polyposis (CRCP); next generation sequencing (NGS); incremental cost-effectiveness ratio (ICER); quality adjusted life year (QALY)

## BACKGROUND

The evaluation of common hereditary conditions in the genetics clinic has changed with the introduction of massive parallel sequencing, also called next generation sequencing (NGS).[1, 2] This technology is better for evaluation of genetically heterogeneous conditions, for example cardiomyopathies, and inherited cancers like breast and colon, which are associated with mutations in different genes.[3-5] The widespread use of NGS in the clinic has been precipitated by a substantial decrease in technology costs and by the creation of more robust gene variant databases.[6] In a time of transition towards clinical exomes and genomes, the most common application of NGS in the genetics clinic is sequencing panels of genes associated with the condition being diagnosed.[7] The amount of genes in the case of cancer range from five to forty, although the tendency as technology becomes cheaper has been to include more of them. [8]However, the utility of testing an eclectic group of genes with different modes of inheritance and with varying levels of disease penetrance is frequently questioned based on the argument that the costs of increased surveillance and unnecessary treatments will outweigh the benefits of cancer prevention, especially for variants of low disease penetrance and the ones with a poor body of evidence.[9, 10]

A common cause of referral to medical genetics clinics is a group of diseases characterized by the presence of colon cancer or polyps, and referred to as colorectal cancer and polyposis (CRCP) syndromes.[11] A strong family history of colon cancer or a personal history of colon cancer, especially at an early age is an indication for referral to a specialized cancer genetics clinic.[12] If the condition is associated with none to a few polyps, one of the CRCP syndromes, Lynch, comes first in the differential diagnosis. The standard clinical evaluation for Lynch syndrome has been centered in ruling out

abnormalities with tumor testing, followed by targeted sequencing of the suspicious gene if there is a protein deficiency. [13, 14] Clinical criteria have been developed to identify patients with a high pretest probability of having Lynch syndrome.[15, 16], but still around 50% of the patients that fulfill the astringent Amsterdam criteria will leave the genetics clinic without an identified Lynch mutation.[17] Based on our own observations, we argue that a significant proportion of the patients referred to the genetics clinic for evaluation of CRCP syndromes, are in fact not Lynch, but other CRCP syndromes that are non-differentiable on a clinical basis, and would go otherwise undiagnosed if we do not test for variants in these other CRCP genes.[18] These CRCP syndromes are an ideal pathology to study the cost-effectiveness of NGS panels because they are a common indication for referral to our clinic, because there are multiple genes associated with an overlapping clinical picture (locus heterogeneity) and because the standard of care has limited sensitivity, even in the face of constricting clinical criteria.

The first objective of this study was to evaluate the cost-effectiveness of NGS panels in the diagnosis of patients referred to the medical genetics clinic with suspected CRCP syndromes, when compared to the standard of care based on current National Comprehensive Cancer Network guidelines. The second objective was to evaluate the incremental benefit of adding groups of CRCP genes to NGS panels based on their associated condition's mode of inheritance (i.e., autosomal dominant vs. autosomal recessive) and the lifetime penetrance of colorectal cancer (i.e., high vs. low).

## **METHODS**

We developed a decision model to estimate the cost-effectiveness of the use of NGS in medical genetics clinics. This is a cost-utility analysis from a healthcare perspective that calculates the costs and benefits of identifying patients referred to the clinic (probands) for CRCP syndrome, in order to identify relatives that also have the mutation and prevent mortality from colorectal cancer via intensive surveillance with colonoscopy. The model uses estimates of direct costs of screening, diagnosis, and health care associated with colorectal cancer from a model developed by Mvundura et al[19], as well as primary data from an academic molecular genetic laboratory to calculate estimates of CRCP allele frequencies.[20] The main audience of our study is medical care providers that evaluate common inherited types of cancer, like medical geneticists and oncologists with a focus of practice in cancer genetics. Another audience is health decision makers, both public and private, that determine resource allocation for testing of conditions with a genetic predisposition.

### **Model overview**

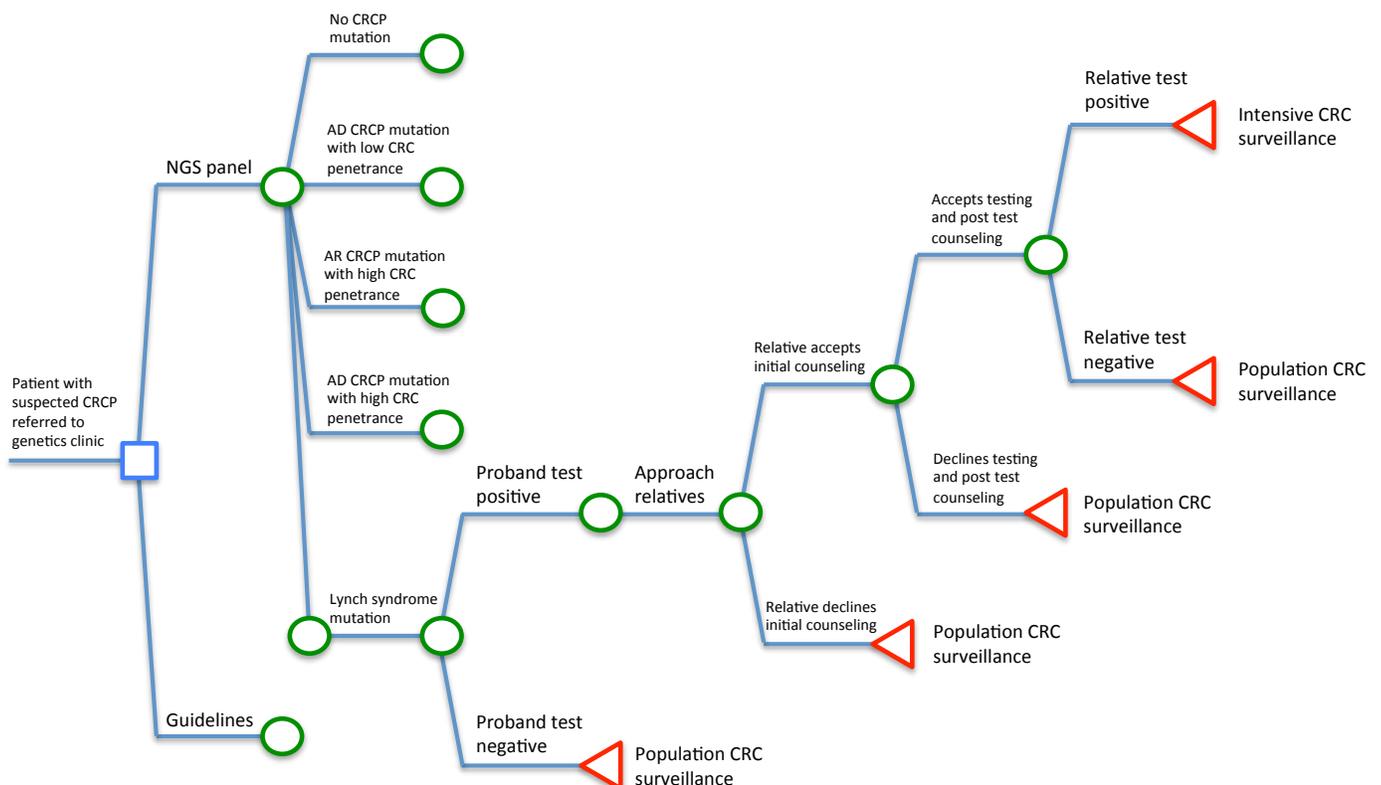
The decision model (Figure 1) compares the standard of care for evaluation of patients with suspected CRCP syndromes versus evaluation by NGS panels. We have used the National Comprehensive Cancer Network (NCCN®) guidelines to establish the standard of care for three reasons: first, they are the most frequently used in medical genetics and cancer genetics settings, second, they make a systematic assessment of each CRCP syndrome, which allows us to exclude patients with typical single gene mutation presentations from our study that could otherwise be evaluated by sequencing just one gene, and third, NGS technologies have been excluded so far in their recommendations, which allows a better capture of the effectiveness of NGS panels for the purpose of

identifying relatives with the mutation. For the purpose of this analysis, the guidelines care for CRCP syndromes is the traditional stepwise approach for evaluation of patients with a personal or family history of colorectal cancer or polyps. These patients frequently receive tumor tissue testing with Immunohistochemistry or microsatellite instability assay, followed by targeted sequencing of the suspected gene, in case a protein deficiency is identified.[13, 14] There is an optional intermediate step of *BRAF* mutation testing in case of an abnormal *MLH1* expression. To make the fairest comparison, we used the most cost-effective strategy according to previous studies, which is tumor testing with immunohistochemistry, followed by reflex tests.[19]

Based on estimates of allele frequencies from an academic molecular genetics laboratory that serves as a national referral center for NGS testing, we classified the CRCP syndrome population in four groups: (1) those with Lynch syndrome mutations, which include patients with mutations in the four mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) and *EPCAM*; (2) patients with autosomal dominant forms of CRCP with high penetrance of colon cancer, which include patients with *APC* mutations (associated with familial adenomatous polyposis and its attenuated form), *BMPR1A* and *SMAD4* mutations (associated with juvenile polyposis syndrome), *STK11* mutations (associated with Peutz-Jeghers); (3) patients with autosomal recessive forms of CRCP and high penetrance of colon cancer, who are patients with *MUTYH* mutations; and (4) patients with autosomal dominant forms of CRCP and low penetrance of colon cancer, which include a heterogeneous group of genes like *PTEN* (associated with Cowden syndrome), *TP53* (associated with LiFraumeni), *CDH1* (associated with diffuse hereditary gastric cancer), and others. If a mutation is identified in the proband, we approached the relatives, and to this end we elaborated two scenarios: in the first one we reached out to first degree relatives, while in the second scenario we contacted first,

second, and third degree relatives. We established these two scenarios because there is a financial and logistical effort to contact more distant relatives, but theoretically that effort comes with higher rewards and is becoming a frequent practice in clinical genetics settings. Provided that the relatives accept counseling and testing, we perform targeted analysis for the mutation identified in the proband. If the relative is found to carry the mutation, then he/she is offered intensive colorectal cancer surveillance with colonoscopy. We calculated the payoffs and costs for each mutation identified in a relative from the model developed by Mvundura et al[19], and to that end we modified the inputs for penetrance of colorectal cancer for the condition, the median age of onset and the initiation of screening colonoscopies.

Figure 1. Decision tree comparing NGS panel versus guidelines for evaluation of patients referred to the clinic for CRCP evaluation.



### **Model Inputs**

The model inputs for our base case and the sensitivity analysis range are illustrated in table 1. The probabilities of having a CRCP related mutation are estimated from the NGS panel database at the Department of Laboratory Medicine at University of Washington (see patient and laboratory data below).[20] Data on sensitivity/specificity of IHC and Sequencing/MLPA, the average number of relatives per proband, as well as the proportion of relatives accepting counseling and accepting testing were obtained from the Supplementary Evidence Review performed as part of the EGAPP pilot program for Lynch syndrome.[21] The amount of relatives approached for patients with autosomal recessive conditions was estimated at half of the autosomal dominant since they usually affect siblings, if any relatives, while the proportion of affected first degree relatives was also estimated to be lower. The Bayesian considerations for relatives that have a diagnosis of the condition were not accounted for since we assumed we would only test undiagnosed relatives. The costs of genetic services were obtained from previous literature and the team of genetic counselors at University of Washington, while the costs of testing were estimated from the billing services of the Department of Laboratory Medicine, also at University of Washington. The outcomes and costs per mutation identified in a relative were obtained by modification of Mvundura's model[19], and modified based on the median age of onset and the penetrance of colorectal cancer for each group of genes. The penetrance estimates and median age of onset were obtained from available literature, including the NCCN® guidelines, and by consensus from a multidisciplinary group of medical geneticists and gastroenterologists at University of Washington.

Table 1. List of model inputs.

PARAMETER	BASE CASE	SENSITIVITY ANALYSIS RANGE	
		LOW	HIGH
Probabilities of carrying CRCP mutation	12.89%	9.21%	16.58%
Probabilities of not carrying CRCP mutation	87.11%	83.42%	90.79%
Probabilities of having Lynch mutation	6.92%	4.13%	9.71%
Probabilities of having Autosomal Dominant CRCP syndrome with high CRC penetrance	2.83%	1.01%	4.65%
Probabilities of having Autosomal Recessive CRCP syndrome with high CRC penetrance	1.26%	0.03%	2.48%
Probabilities of having Autosomal Dominant CRCP syndrome with low CRC penetrance	1.89%	0.39%	3.38%
Average number of first-degree relatives per proband, AD conditions	4	2	8
Average number of first-degree relatives per proband, AR conditions	2	1	4
Average number of first/second/third degree relatives per proband, AD conditions	12	4	20
Average number of first/second/third degree relatives per proband, AR conditions	6	2	10
Proportion of first-degree relatives with the mutation, AD conditions	45%	40%	50%
Proportion of first-degree relatives with the mutation, AR conditions	25%	20%	30%
Proportion of first/second/third degree relatives with the mutation, AD conditions	35%	30%	40%
Proportion of first/second/third degree relatives with the mutation, AR conditions	15%	10%	20%
Proportion of relatives accepting genetic counseling	52%	34%	70%
Proportion of relatives counseled accepting genetic testing	95%	89%	99%
IHC sensitivity for LS	83.0%	63.0%	96.0%
IHC specificity for LS	88.8%	83.0%	94.0%
Sequencing/MLPA sensitivity for LS	99.5%	98.6%	99.9%
Sequencing/MLPA (1-specificity) for LS	0.040%	0.005%	0.100%
IHC sensitivity for non-Lynch CRCP	3.0%	0.0%	10.0%
IHC specificity for non-Lynch CRCP	100.0%		
NGS gene panel sensitivity	99.9%	99.5%	100.0%
NGS gene panel specificity	99.9%	99.8%	100.0%
Targeted mutation testing specificity	100.0%		
Life years gained per relative with Lynch patient detected	1.0678	0.704748	1.54831
QALYs gained per relative with Lynch patient detected	0.904	0.59664	1.3108
Life years gained per relative with AD CRCP syndrome with high CRC penetrance detected	1.5717	1.037322	2.278965
QALYs gained per relative with AD CRCP syndrome with high CRC penetrance detected	1.3254	0.874764	1.92183
Life years gained per relative with AR CRCP syndrome with high CRC penetrance detected	1.5717	1.037322	2.278965
QALYs gained per relative with AR CRCP syndrome with high CRC penetrance detected	1.3254	0.874764	1.92183
Life years gained per relative with AD CRCP syndrome with low CRC penetrance detected	0.2481	0.163746	0.359745
QALYs gained per relative with AD CRCP syndrome with low CRC penetrance detected	0.2103	0.138798	0.304935
Cost of IHC analysis	\$261	\$174	\$377
Cost of sequencing one gene	\$600	\$396	\$870
Cost of next-gene sequencing panel	\$2,700	\$1,782	\$3,915
Cost of initial counseling before genetic testing	\$174	\$114	\$245
Cost of post-test genetic counseling	\$95	\$63	\$137
Cost of approaching each relative	\$25	\$15	\$35
Cost of sequencing for family mutation in relative	\$55	\$37	\$80
Costs of surveillance and treatment per relative with Lynch syndrome detected	\$16,437	\$10,848	\$23,834
Costs of surveillance and treatment per relative with AD CRCP syndrome with high CRC penetrance detected	\$12,652	\$8,350	\$18,345
Costs of surveillance and treatment per relative with AR CRCP syndrome with high CRC penetrance detected	\$12,652	\$8,350	\$18,345
Costs of surveillance and treatment per relative with AD CRCP syndrome with low CRC penetrance detected	\$18,644	\$12,305	\$27,034
Discount rate	3%	0%	5%
Penetrance of high CRC risk mutations	70	40	90
Penetrance of low CRC risk mutations	10	5	30
Median age of diagnosis, high CRC penetrance mutations	50	30	70
Median age of diagnosis, low CRC penetrance mutations	50	30	70

## **Patient and laboratory data**

Estimates of allelic probabilities were obtained from the working database of clinical next-generation sequencing that is used in the Department of Laboratory Medicine at University of Washington.[20] A quality assurance specialist with HIPAA clearance reviewed the samples sent for evaluation with an NGS panel (ColoSeq™) specific for patients with suspected CRCP syndrome. The NGS panel has been offered since October 2011, and currently reads intronic and exonic sequences of 19 genes associated with CRCP (see appendix A). After removing samples used for non-clinical purposes, a new sheet with new laboratory ID numbers was generated for de-identification purposes and sent to the principal investigator. The clinical history was obtained from genetic counselors at the time of referral and was used by the investigator to exclude non-eligible patients. Exclusion criteria were minors, patients with a mutation already identified in their family, and patients with a clinical presentation consistent with a single gene mutation, such as familial adenomatous polyposis, Cowden syndrome or Peutz-Jeghers syndrome. We excluded patients with more than 20 polyps, since arguably these individuals should be sequenced for MUTYH and/or APC genes only.[7] All procedures were approved by the Institutional Review Board of University of Washington and HIPAA regulations followed.

## **Outcomes**

The probabilities for each outcome were calculated from the decision tree, and we assigned health outcomes and costs of surveillance and treatment of colorectal cancer for each relative with a mutation identified from Mvundura's model[19]. We then calculated total costs, life years gained and quality adjusted life years (QALY) for the evaluation of each group of genes. We decided to obtain QALY as well as life years

gained as is recommended in cost-effectiveness analysis, although for life-saving measures there is little difference which measure is used.[22, 23]

## **Analysis**

The analysis took place in two phases. First, we compared the added cost and the added benefits of an NGS panel that contained all CRCP genes compared to a workup based in guidelines and calculated the Incremental Cost-Effectiveness Ratio (ICER) to estimate the cost per life year and per QALY.

The second part of the analysis consisted on the calculation of ICER for four hypothetical NGS panels, comparing the first one with the standard of care and the others with the previous panel in the list:

- Panel 1: includes only the genes associated with Lynch syndrome, which are most commonly associated with CRCP syndromes as a group
- Panel 2: includes the Lynch syndrome genes, as well as genes associated with autosomal dominant CRCP syndromes with high penetrance of colorectal cancer
- Panel 3: includes all the genes in panel 2, and also genes associated with autosomal recessive CRCP syndromes with high penetrance of colorectal cancer
- Panel 4: includes the genes in panel 3, and genes associated with autosomal dominant CRCP syndromes with low penetrance of colorectal cancer

This sequential organization of NGS panels makes sense because larger panels are expected to be more effective, and because panels tend to include genes with a high penetrance first and then move on to genes with lower penetrance or with less supportive evidence in the literature.

To evaluate the stability of our conclusions, the study was complemented by a one-way sensitivity analysis to our model inputs, and presented these results in a tornado diagram.

## RESULTS

The evaluation of a patient with suspected CRCP syndromes with an NGS panel represents an average extra cost of \$3,300 at an average gain 0.06 life years gained and 0.05 QALYs. This extra cost comes from the more expensive test and the process of contacting, screening, and testing more relatives when using an NGS panel. The ICER calculation is displayed in Table 2. The investment for the first scenario, where only first-degree relatives are tested results in \$55,000 per life year gained and \$66,000 per QALY, while contacting first, second and third degree relatives results in \$34,000 per life year gained and \$40,000 per QALY.

The results of comparison of the four panels, starting with Panel 1 versus guidelines followed by the next more comprehensive panel is shown in Table 3. When evaluating the incremental benefit of sequencing only the Lynch syndrome genes (Panel 1), the cost per QALY in the first and second scenarios exceeds \$100,000. However, once autosomal dominant genes with a high disease penetrance are included in the panel, the cost per QALY drops to \$69,000 and \$38,000 in the first and second scenario respectively, and the addition of autosomal recessive genes to the panel is even more cost effective with ICER as low as \$14,000 per QALY. Finally, the least benefits are obtained from the addition of variants with a low penetrance, but because the downstream costs are still relatively low (around \$700 per person evaluated), this represents ICER below \$100,000 per QALY.

Table 2. Incremental Comparative Effectiveness Ratio (ICER) of complete NGS panel compared to NCCN® guidelines.

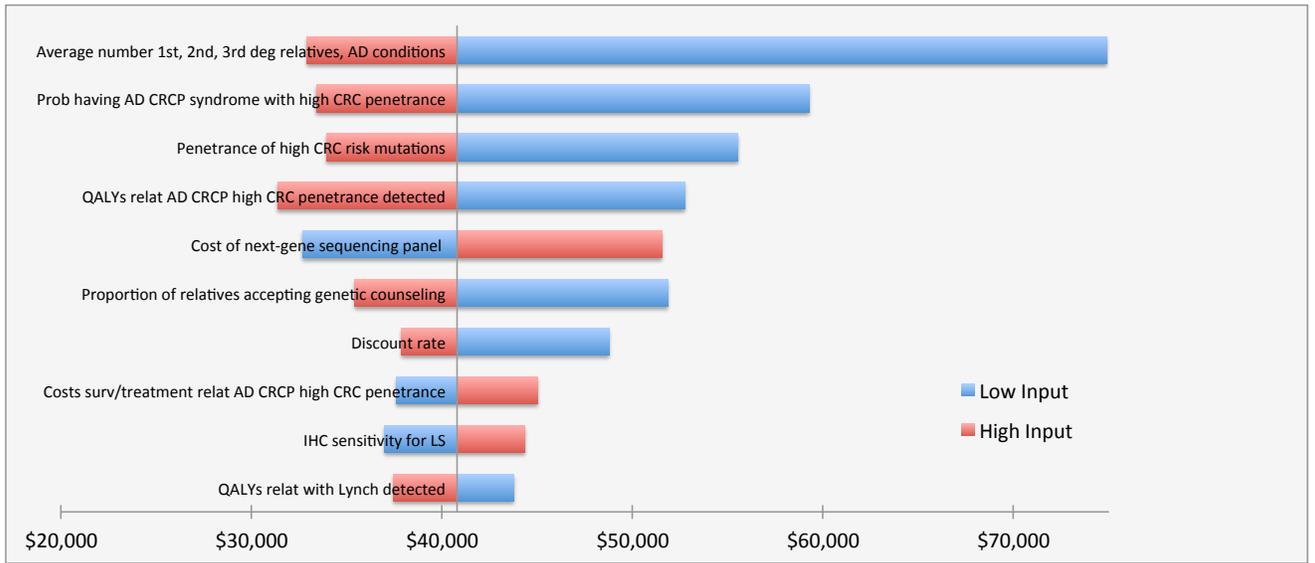
ICER of full NGS panel (ColoSeq) compared to current evaluation by guidelines	First scenario (1st degree relatives approached only)	Second scenario (1st, 2nd and 3rd degree relatives approached)
Dollars per Life years saved	\$55,633.92	\$34,049.67
Dollars per QALY saved	\$65,899.72	\$40,331.82

Table 3. ICER comparing panel 1 with guidelines and each panel with the previous.

Panel description		ICER per panel compared to guidelines (Panel1) or previous panel in dollars per QALY	
		First scenario	Second scenario
Panel 1	Lynch syndrome genes only	\$262,875	\$124,314
Panel 2	Panel 1 plus Autosomal Dominant CRCP syndromes with high CRC Penetrance	\$69,374	\$38,463
Panel 3	Panel 2 plus Autosomal Recessive CRCP syndromes with high CRC penetrance	\$14,081	\$15,201
Panel 4	Panel 3 plus Autosomal Dominant CRCP syndromes with low CRC penetrance	\$84,048	\$85,730

The sensitivity analysis results are pictured in a tornado diagram (Fig.2). In this analysis the conclusions remain unchanged and no variable modification would result in an incremental cost superior to \$80,000 per QALY in the second scenario. The variables that reflect more uncertainty are the average number of relatives approached, the probabilities of having a highly penetrant autosomal dominant variant and the QALYs assigned to these variants. Also the penetrance of colorectal cancer for the type of mutation was important, as well as the cost of the NGS panel.

Figure 2. Tornado diagram of one-way sensitivity analysis.



## DISCUSSION

In this study we have developed a decision model to evaluate the cost-effectiveness of NGS panels for the diagnosis of patients referred to the medical genetics clinic with suspected CRCP syndromes. We also evaluated the cost-effectiveness of adding groups of genes to the panel, based on their mode of inheritance and the penetrance of colorectal cancer.

The results show that NGS panels in the evaluation of CRCP syndromes are very cost-effective compared to guideline recommendations, and most of the benefit is driven by finding variants in genes associated with autosomal dominant types of CRCP with a high penetrance of colorectal cancer. The results confirm that obtaining information in genes related to Lynch syndrome alone with the current price of next generation sequencing is not economically justifiable, but if genes with associated autosomal dominant, highly penetrant conditions are added to the panel, then including other genes, even if they have an autosomal recessive inheritance or low penetrance of colorectal cancer is also cost-effective, because it translates into partial benefits for the same or slightly higher costs.

The first implication of this article is that NGS panels might be currently underutilized for the evaluation of CRCP syndromes. This could be due to a scarcity of literature on cost-effectiveness of NGS technologies in specialized genetics clinics, to a perceived high price of genetic technologies for intangible benefits among providers and payers, and reimbursement obstacles from payers that request more evidence of clinical benefits for the application of novel diagnostic tools. The second implication is that more comprehensive technology, at least in this scenario, seems to represent a good

investment, and the inclusion of more genes in the clinical evaluation of clinically similar conditions, can translate in better health. Finally, approaching more distant relatives to discuss a family history of CRCP syndromes brings significant health benefits for the financial and logistical effort.

This is the first study showing that NGS panels are cost-effective as a first step in the evaluation of a common inherited condition. This study should help future researchers to investigate the cost-effectiveness of NGS panels on the evaluation of other cancer phenotypes, like breast cancer, and non-cancer phenotypes, like cardiomyopathies. It should also encourage the cost-effectiveness evaluation of more comprehensive uses of NGS technologies, such as exome and genome sequencing, which are not indicated for common inherited diseases of the adult at the moment.

Previous studies evaluating the role of sequencing technologies as a first diagnostic step in the evaluation of Lynch and other CRCP syndromes resulted in costs varying from \$700,000 to several million dollars per QALY, which is nonviable.[19, 24] However, these studies were in a universal setting, where every patient diagnosed with colorectal cancer would receive a germline sequencing test, unlike our population of referred patients that are enriched for CRCP mutations. Also, technology has become cheaper in the last few years, when these studies took place.

Our study has several limitations. First, we make a very strong assumption when we compare the penetrance of pathogenic/likely pathogenic variants to the penetrance that is described in the literature for these conditions. A current review of the literature shows very limited data to establish the lifetime penetrance of colorectal cancer for patients diagnosed with some types of CRCP syndromes, and the data is almost absent when

trying to obtain the penetrance for patients that have a variant in a given gene. Second, the limited sample size that is uniform in genomic studies is no exception in ours, and we could only address it partially with the sensitivity analysis. Only future studies on the allelic probabilities with more patients may confirm our estimates. A third important limitation is the heterogeneous referral population that we see in specialized cancer genetics clinics, since not all of the patients evaluated will actually get tumor tissue testing as the first test, and may instead get gene sequencing directly. Finally, there are limitations in terms of the clinical information obtained from diagnostic samples, and we are basing the exclusion criteria on the clinical information obtained by genetic counselors at the time of referral. More detailed information, such as the amount of polyps found during every colonoscopy in the medical history is seldom available.

In summary, we developed a decision model to evaluate the cost-effectiveness of NGS panels for the evaluation of CRCP syndromes in the genetics clinic, and found that NGS panels are very cost-effective in this setting. Future studies need to determine if these findings are applicable to other common phenotypes and to other, more comprehensive NGS technologies. Although several limitations lay ahead in the incorporation of NGS in clinical care, more robust databases and cheaper technology are making genomic tests a viable initial diagnostic alternative.

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## APPENDIX

Appendix A. List of CRCP syndromes and associated genes tested by NGS panel (ColoSeq).

Disease name or cancer risk	Associated gene
Lynch syndrome, Muir-Torre	MLH1
	MSH2
Lynch syndrome	PMS2
	MSH6
	EPCAM
Attenuated familial adenomatous polyposis, Turcot syndrome	APC
MUTYH associated polyposis	MUTYH
Juvenile adenomatous polyposis	BMPR1A
	SMAD4
Cowden syndrome	PTEN
Hereditary diffuse gastric cancer	CDH1
Li Fraumeni	TP53
Colon cancer	GALNT12
Peutz-Jeghers	STK11
Colon cancer, endometrial cancer	POLE
Colon cancer	POLD1
Polyposis	GREM1
Breast cancer, thyroid cancers, macrocephaly	AKT1
Breast cancer, thyroid cancers, macrocephaly	PIK3CA