Next-Generation Sequencing Panels for the Diagnosis of Colorectal Cancer and Polyposis Syndromes: A Cost-Effectiveness Analysis

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Published online ahead of print at www.jco.org on May 4, 2015.

Supported by Patient-Centered Outcomes Research Career Development Program from the Agency for Healthcare Research and Quality/University of Washington Grant No. K12 HS021686 (C.J.G.), Grants No. U01HG0006507 and U01HG007307 from the National Human Genome Research Institute and National Cancer Institute (G.P.J.), and Grant No. U01AG047109 from the National Institutes of Health Common Fund/National Institute of Aging (D.L.V.).

Terms in [blue](#) are defined in the glossary, found at the end of this article and online at www.jco.org.

Presented, in part, at the 64th Annual Meeting of the American Society of Human Genetics, San Diego, CA, October 18-22, 2014.

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

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0732-183X/15/3318w-2084w/\$20.00

DOI: 10.1200/JCO.2014.59.3665

ABSTRACT

Purpose

To evaluate the cost effectiveness of next-generation sequencing (NGS) panels for the diagnosis of colorectal cancer and polyposis (CRCP) syndromes in patients referred to cancer genetics clinics.

Patients and Methods

We developed a decision model to evaluate NGS panel testing compared with current standard of care in patients referred to a cancer genetics clinic. We obtained data on the prevalence of genetic variants from a large academic laboratory and calculated the costs and health benefits of identifying relatives with a pathogenic variant, in life-years and quality-adjusted life-years (QALYs). We classified the CRCP syndromes according to their type of inheritance and penetrance of colorectal cancer. One-way and probabilistic sensitivity analyses were conducted to assess uncertainty.

Results

Evaluation with an NGS panel that included Lynch syndrome genes and other genes associated with highly penetrant CRCP syndromes led to an average increase of 0.151 year of life, 0.128 QALY, and \$4,650 per patient, resulting in an incremental cost-effectiveness ratio of \$36,500 per QALY compared with standard care and a 99% probability that this panel was cost effective at a threshold of \$100,000 per QALY. When compared with this panel, the addition of genes with low colorectal cancer penetrance resulted in an incremental cost-effectiveness ratio of \$77,300 per QALY.

Conclusion

The use of an NGS panel that includes genes associated with highly penetrant CRCP syndromes in addition to Lynch syndrome genes as a first-line test is likely to provide meaningful clinical benefits in a cost-effective manner at a \$100,000 per QALY threshold.

J Clin Oncol 33:2084-2091. © 2015 by American Society of Clinical Oncology

INTRODUCTION

A common indication for referral to cancer genetics clinics is evaluation for hereditary colorectal cancer and polyposis (CRCP) syndromes, a group of diseases characterized by a strong personal and/or family history of colon cancer and/or polyps, especially if present at an early age.^{1,2} Lynch syndrome leads the differential diagnosis if the condition is associated with few to no polyps and the presentation is not consistent with CRCP syndromes caused by mutations in one specific gene.³⁻⁶ Multiple sets of clinical criteria have been developed to screen patients with CRCP with high risk of having Lynch syndrome, including the Amsterdam and Bethesda criteria,⁷⁻⁹

but neither set of criteria is particularly accurate, and the sensitivity and specificity are generally regarded as unacceptable.¹⁰⁻¹² Consequently, some institutions are adopting universal Lynch syndrome screening in all patients diagnosed with colorectal cancer.¹³

The evaluation of inherited cancer syndromes is changing with the introduction of massively parallel sequencing, also called next-generation sequencing (NGS).¹⁴⁻¹⁶ Despite the promise of NGS, the utility of testing multiple genes with different modes of inheritance and with varying levels of disease [penetrance](#) has been questioned based on the argument that the costs of increased surveillance and unnecessary treatments may outweigh the benefits of cancer prevention, as well as the uncertain

consequences of the identification of variants of unknown significance.^{17,18} The CRCP phenotype is an ideal model to study the cost-effectiveness of NGS panels because it is a common indication for referral to our genetic medicine clinic; there are multiple genes associated with an overlapping clinical picture (locus heterogeneity), and testing under the current standard of care has unacceptable sensitivity.¹⁰⁻¹²

The primary objective of this study was to perform a **cost-effectiveness analysis** of an NGS panel in the diagnosis of patients evaluated for suspected genetic CRCP syndromes in the medical genetics clinic compared with the sequential evaluation for Lynch syndrome recommended by current guidelines.¹³ Secondary objectives were to evaluate the impact of universal Lynch syndrome screening on our results and to evaluate the cost effectiveness of NGS panel testing for universal screening in all patients with colorectal cancer.

PATIENTS AND METHODS

Model Overview

We developed a decision model to estimate the immediate and downstream costs and benefits of NGS panel testing of patients referred to the clinic (**probands**) for evaluation of CRCP syndrome and of colorectal cancer surveillance with colonoscopy in family members of patients identified to have a pathogenic variant in a CRCP gene (Fig 1). We used estimates of direct costs of screening, diagnosis, and health care associated with colorectal cancer

screening and treatment from a Centers for Disease Control and Prevention model developed by Mvundura et al,¹⁹ as well as primary data from an academic molecular genetics laboratory to calculate estimates of CRCP variant frequencies.²⁰

The standard of care in this context is a diagnostic protocol that begins with immunohistochemistry of colon cancer tissue followed by one of the following: no further testing if normal; if abnormal, *MLH1* staining and rule-out testing of somatic variants in the *BRAF* gene and, if no mutations found, reflex sequencing of the *MLH1* gene; or if abnormal staining of *MSH2*, *MSH6*, or *PMS2*, sequencing of the respective gene as the final diagnostic step.^{7,9,13,21} This testing protocol has been shown to be a cost-effective approach to Lynch syndrome screening.^{19,22-25}

In the NGS strategy, we classified patients with suspected inherited CRCP into one of the following five categories based on the distribution of pathogenic or likely pathogenic variants (Appendix Table A1, online only) according to the Department of Laboratory Medicine at the University of Washington²⁰: patients with no pathogenic/likely pathogenic variants; those with pathogenic/likely pathogenic variants in Lynch syndrome genes, which include the four mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) and *EPCAM*; patients with other high-penetrance autosomal dominant hereditary CRCP syndromes, which includes patients with *APC* (associated with familial adenomatous polyposis and its attenuated form), *BMPRIA* and *SMAD4* (associated with juvenile polyposis syndrome), and *STK11* (associated with Peutz-Jeghers syndrome) pathogenic/likely pathogenic variants; patients with high-penetrance autosomal recessive CRCP syndromes, which includes patients with *MUTYH* pathogenic/likely pathogenic variants; and patients with low-penetrance autosomal dominant CRCP syndromes, which

Fig 1. Decision tree comparing the next-generation sequencing (NGS) panel versus guidelines for evaluation of patients referred to the medical genetics clinic for colorectal cancer and polyposis (CRCP) syndrome evaluation. The decision node (square) indicates a decision point between the two alternative options, whereas the chance nodes (circles) show where two or more alternative events for a patient are possible. Pathways are mutually exclusive sequences of events, and a probability is assigned to each path. Multiplying probabilities along pathways estimates the probability that a relative with the CRCP mutation in question is identified and can therefore receive intensive colorectal cancer (CRC) surveillance (triangles). Only the paths for patients with variants associated with Lynch syndrome are illustrated. AD, autosomal dominant; AR, autosomal recessive. See Appendix (online only) for details.

includes patients with a heterogeneous group of genes such as *PTEN* (associated with Cowden's syndrome), *TP53* (associated with Li-Fraumeni syndrome), *CDH1* (associated with diffuse hereditary gastric cancer), and others. The concept of penetrance for this classification was applied only in regard to the incidence of colorectal cancer and not to other cancers associated with the syndrome. We grouped pathogenic and likely pathogenic variants because they are clinically actionable and did not include variants of unknown significance.

In our base-case analysis, we assumed that first-, second-, and third-degree relatives would be contacted and ran a scenario analysis in which only first-degree relatives would be approached. If the relatives hypothetically accepted counseling and testing, we assumed that they would undergo targeted analysis for the pathogenic variant identified in the proband. If the relative was found to carry the pathogenic variant, then he or she was presumably offered intensive colorectal cancer surveillance with colonoscopy at recommended intervals.

Model Inputs

The model parameters are listed in [Table 1](#) and discussed in the Appendix (online only).

Analysis

The primary outcomes were total health care costs, life-years gained, and quality-adjusted life-years (QALYs). We evaluated the following four hypothetical NGS panels organized in order of increasing effectiveness, where each panel was larger than the previous one: panel 1: includes only the Lynch syndrome genes; panel 2: panel 1 plus genes associated with autosomal dominant CRCP syndromes with high penetrance of colorectal cancer; panel 3: panel 2 plus genes associated with autosomal recessive CRCP syndromes with high penetrance of colorectal cancer; and panel 4: panel 3 plus genes associated with autosomal dominant CRCP syndromes with low penetrance of colorectal cancer but not necessarily with other syndromes.

We used this sequential organization of NGS panels because panels tend to include genes with a high penetrance of disease first, and subsequently include genes with lower penetrance or with less supportive evidence of gene-disease association. We created these hypothetical panels to also effectively capture the incremental benefit and costs associated with the return of information from each gene group.

We conducted one-way sensitivity analysis to evaluate the effect of changing each of the variables in our model one at a time. We conducted probabilistic sensitivity analysis to quantify the level of confidence in the conclusions of our evaluation.

In addition to the scenario analysis in which only first-degree relatives were contacted, we conducted a scenario analysis to evaluate the impact of universal Lynch syndrome screening programs on our findings. For that purpose, we removed patients with Lynch syndrome pathogenic variants from the analysis (with the exception of false-negative results in universal screening) and reduced the costs of standard of care to the clinic visit.

Finally, we conducted a scenario analysis to evaluate the cost-effectiveness of NGS panels as a universal screening test in all patients diagnosed with colorectal cancer. In this analysis, we used the reported frequency of Lynch syndrome pathogenic variants in the universal population of patients with colorectal cancer²⁷ and calculated a ratio between the frequency of Lynch variants in our referral population and the universal population to estimate the frequency of non-Lynch syndrome pathogenic variants in the universal population.

icantly higher than the contemporary and commonly cited threshold of \$100,000 per QALY.³⁰ However, the addition of genes associated with highly penetrant autosomal dominant and autosomal recessive CRCP syndromes (panel 3) resulted in a substantial life expectancy gain of 0.151 year and 0.128 QALY per person, at an increased cost of approximately \$4,650, which represented an incremental cost-effectiveness ratio (ICER) of \$36,500 per QALY compared with standard of care. Panels 1 and 2 are under extended dominance of panel 3 because they result in fewer QALYs gained per dollar spent. Finally, the incremental gain of adding genes associated with low-penetrance CRCP syndromes (panel 4) resulted in modest gains of 0.010 life-year, or 0.009 QALY, at a relatively small cost of \$672, which resulted in an ICER of \$77,300 per QALY compared with panel 3, the next best nondominated strategy.

The one-way sensitivity analysis results are shown in a tornado diagram ([Fig 2](#)). The variables that most influenced model outcomes were the average number of relatives approached, the QALYs gained in each identified relative of a patient with a highly penetrant CRCP syndrome, the disease penetrance in patients with highly penetrant CRCP syndromes, the probability of having a variant in a gene associated with a highly penetrant type of CRCP syndrome, the cost of the NGS panel, and the proportion of relatives accepting genetic counseling. No single input modification over the specified ranges resulted in an incremental cost per QALY gained greater than \$80,000 per QALY.

Results of the probabilistic sensitivity analysis for an NGS panel with genes associated with highly penetrant CRCP syndromes (panel 3) compared with standard of care showed average increased life-years (95% credible range, 0.05 to 0.33 life-year) and QALYs (95% credible range, 0.04 to 0.28 QALY) per patient referred to the clinic (proband), with an increased cost (95% credible range, \$2,619 to \$7,625) per patient. The cost-effectiveness acceptability curve illustrates an estimated 74.6% probability that panel 3 is cost effective at threshold of \$50,000 per QALY compared with standard of care and a 99.0% probability of being cost effective at a threshold of \$100,000 per QALY ([Fig 3](#)).

The scenario analysis in which only first-degree relatives were contacted resulted in an ICER of \$59,700 per QALY for panel 3 compared with standard of care and of \$75,400 per QALY for panel 4 when compared with panel 3 ([Appendix Table A2](#), online only). The scenario analysis of NGS panel testing in a population referred to a specialized clinic after universal screening for Lynch syndrome showed an ICER of \$39,300 per QALY for panel 3 compared with standard of care and of \$77,300 per QALY for panel 4 compared with panel 3 ([Appendix Table A3](#), online only). The scenario analysis in which the NGS panel was used for universal testing on all patients with colorectal cancer resulted in an ICER of \$70,600 per QALY for panel 3 compared with standard of care and of \$77,300 per QALY for panel 4 compared with panel 3 ([Appendix Table A4](#), online only).

RESULTS

The projected outcomes of our base-case analysis are listed in [Table 2](#). The results reflect a comparison of each panel with the standard of care or the next best strategy. When evaluating the incremental benefit of sequencing only the Lynch syndrome genes (panel 1) compared with standard of care, the cost per QALY is approximately \$144,200, signif-

DISCUSSION

We developed a decision model to evaluate the cost effectiveness of using NGS panels for the diagnosis of patients referred to the medical genetics clinic with suspected inherited CRCP syndromes. We evaluated the cost effectiveness of adding groups of genes to the panel based on their mode of inheritance and penetrance of colorectal cancer.

Table 1. Model Inputs and Sensitivity Analysis Range

Parameter	Base Case	Sensitivity Analysis Range		Source
		Low	High	
Clinical data				
Probability of not carrying CRCP mutation, %	84.6	80.8	88.4	UWLM ^{20,26}
Probability of carrying CRCP mutation, %	15.4	11.6	19.2	UWLM ^{20,26}
Probability of having Lynch mutation, %	8.5	5.6	11.5	UWLM ^{20,26}
Probability of having AD CRCP syndrome with high CRC penetrance, %	3.7	1.7	5.7	UWLM ^{20,26}
Probability of having AR CRCP syndrome with high CRC penetrance, %	1.1	0.0	2.3	UWLM ^{20,26}
Probability of having AD CRCP syndrome with low CRC penetrance, %	2.0	0.5	3.5	UWLM ^{20,26}
Proportion of LS with <i>MLH1</i> mutation, %	32	18	46	EGAPP ²⁷
Proportion of LS with <i>MSH2</i> mutation, %	39	27	51	EGAPP ²⁷
Proportion of LS with <i>MSH6</i> mutation, %	14	6	22	EGAPP ²⁷
Proportion of LS with <i>PMS2</i> mutation, %	15	7	23	EGAPP ²⁷
Average No. of relatives per proband, AD conditions	12	4	20	EGAPP, ²⁷ Mvundura et al ¹⁹
Average No. of relatives per proband, AR conditions	6	2	10	EGAPP, ²⁷ Mvundura et al ¹⁹
Average No. of relatives per proband, first-degree relatives only scenario, AD conditions	4	2	8	EGAPP, ²⁷ Mvundura et al ¹⁹
Average No. of relatives per proband, first degree relatives only scenario, AR conditions	2	1	4	EGAPP, ²⁷ Mvundura et al ¹⁹
Proportion of relatives with the mutation, AD conditions, %	35	30	40	UWMG, Mvundura et al ¹⁹
Proportion of relatives with the mutation, AR conditions, %	15	10	20	UWMG, Mvundura et al ¹⁹
Proportion of relatives with the mutation alternative scenario, AD conditions, %	45	40	50	UWMG, Mvundura et al ¹⁹
Proportion of relatives with the mutation alternative scenario, AR conditions, %	25	20	30	UWMG, Mvundura et al ¹⁹
Proportion of relatives accepting genetic counseling, %	52	34	70	EGAPP ²⁷
Proportion of relatives counseled accepting genetic testing, %	95	89	99	EGAPP ²⁷
Reduction in CRC risk with increased surveillance, %	62	50	74	EGAPP ²⁷
Reduction in mortality rate with increased surveillance, %	67	54	80	EGAPP ²⁷
Penetrance of high CRC risk mutations, %	70	40	90	UWMG, GeneReviews ²⁸
Penetrance of low CRC risk mutations, %	10	5	30	UWMG, GeneReviews ²⁸
Median age of diagnosis, high CRC penetrance mutations, years	50	30	70	UWMG, GeneReviews ²⁸
Median age of diagnosis, low CRC penetrance mutations, years	50	30	70	UWMG, GeneReviews ²⁸
Laboratory data, %				
IHC sensitivity for LS	83.0	73.0	100.0	EGAPP, ²⁷ Snowsill et al ²²
IHC specificity for LS	88.8	12.5	100.0	EGAPP, ²⁷ Snowsill et al ²²
Sequencing/MLPA sensitivity for LS	99.5	98.6	99.9	EGAPP, ²⁷ Snowsill et al ²²
Sequencing/MLPA (1-specificity) for LS	0.04	0.01	0.10	EGAPP, ²⁷ Snowsill et al ²²
<i>BRAF</i> sensitivity for IHC <i>MLH1</i>	69.0	50.0	85.0	EGAPP, ²⁷ Snowsill et al ²²
<i>BRAF</i> specificity for IHC <i>MLH1</i>	99.0	98.0	99.7	EGAPP, ²⁷ Snowsill et al ²²
IHC sensitivity for non-Lynch CRCP	10.0	5.0	20.0	UWMG, UWLM ^{20,26}
IHC specificity for non-Lynch CRCP	100.0	90.0	100.0	UWMG, UWLM ^{20,26}
Targeted mutation testing specificity	100.0	99.0	100.0	UWMG, UWLM ^{20,26}
NGS gene panel sensitivity	99.9	99.5	100.0	UWMG, UWLM ^{20,26}
NGS gene panel specificity	99.9	99.8	100.0	UWMG, UWLM ^{20,26}
Impact on relatives				
Life-years gained per relative with Lynch patient detected	1.070	0.700	1.550	Mvundura et al ¹⁹
QALYs gained per relative with Lynch patient detected	0.900	0.600	1.310	Mvundura et al ¹⁹
Life-years gained per relative with AD CRCP syndrome with high CRC penetrance detected	1.570	1.040	2.280	Mvundura et al ¹⁹
QALYs gained per relative with AD CRCP syndrome with high CRC penetrance detected	1.330	0.870	1.920	Mvundura et al ¹⁹
Life-years gained per relative with AR CRCP syndrome with high CRC penetrance detected	1.570	1.040	2.280	Mvundura et al ¹⁹
QALYs gained per relative with AR CRCP syndrome with high CRC penetrance detected	1.330	0.870	1.920	Mvundura et al ¹⁹
Life-years gained per relative with AD CRCP syndrome with low CRC penetrance detected	0.250	0.160	0.360	Mvundura et al ¹⁹
QALYs gained per relative with AD CRCP syndrome with low CRC penetrance detected	0.210	0.140	0.300	Mvundura et al ¹⁹

(continued on following page)

Table 1. Model Inputs and Sensitivity Analysis Range (continued)

Parameter	Base Case	Sensitivity Analysis Range		Source
		Low	High	
Cost data				
Cost of NGS panel, \$	2,700	1,782	3,915	UWMG, UWLM billing services, Mvundura et al ¹⁹
Cost of sequencing one gene, \$	600	396	870	UWMG, UWLM billing services, Mvundura et al ¹⁹
Cost of sequencing for family mutation in relative, \$	63	41	91	UWMG, UWLM billing services, Mvundura et al ¹⁹
Cost of IHC analysis, \$	298	197	433	UWMG, UWLM billing services, Mvundura et al ¹⁹
Cost of <i>BRAF</i> V600E mutation testing, \$	71	48	102	UWMG, UWLM billing services, Mvundura et al ¹⁹
Cost of initial counseling before genetic testing, \$	199	131	288	UWMG, UWLM billing services, Mvundura et al ¹⁹
Cost of post-test genetic counseling, \$	109	72	157	UWMG, UWLM billing services, Mvundura et al ¹⁹
Cost of approaching each relative, \$	25	15	35	UWMG, UWLM billing services, Mvundura et al ¹⁹
Costs of surveillance and treatment per relative with LS detected, \$	18,787	12,400	27,242	Mvundura et al ¹⁹
Costs of surveillance and treatment per relative with AD CRCP syndrome with high CRC penetrance detected, \$	21,310	14,065	30,900	Mvundura et al ¹⁹
Costs of surveillance and treatment per relative with AR CRCP syndrome with high CRC penetrance detected, \$	21,310	14,065	30,900	Mvundura et al ¹⁹
Costs of surveillance and treatment per relative with AD CRCP syndrome with low CRC penetrance detected, \$	14,461	9,544	20,969	Mvundura et al ¹⁹
Discount rate, %	3	0	5	Gold et al ²⁹

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; CRC, colorectal cancer; CRCP, colorectal cancer and polyposis syndromes; EGAPP, Evaluation of Genomic Applications in Practice and Prevention; IHC, immunohistochemistry; LS, Lynch syndrome; MLPA, multiplex ligation-dependent probe amplification; NGS, next-generation sequencing; QALY, quality-adjusted life-year; UWLM, University of Washington Department of Laboratory Medicine; UWMG, University of Washington Multidisciplinary and Medical Genetics Group.

Our results indicate that the addition of genes associated with high-penetrance CRCP syndromes leads to a highly cost-effective gene panel (eg, below the historical \$50,000 per QALY threshold), whereas addition of genes associated with low-penetrance CRCP syndromes leads to a gene panel that remains cost effective, but less so (eg, below the contemporary \$100,000 per QALY threshold).³⁰ These panels

remain cost effective at a threshold of \$100,000 per QALY in an alternative scenario analysis where only first-degree relatives are tested. The results confirm that sequencing Lynch syndrome genes alone at the current price of NGS is not cost effective, but if other genes associated with high-penetrance CRCP syndromes are added to the panel, the intervention is cost effective. Although the life-year benefits

Table 2. Incremental Cost-Effectiveness Ratio and Differences in Payoffs When Comparing Each Hypothetical Panel With Standard of Care or the Next Most Effective Strategy

Measure	Panel 1	Panel 2	Panel 3	Panel 4
Compared with standard of care				
Δ Life-years	0.023	0.143	0.151	0.161
Δ QALY	0.019	0.121	0.128	0.136
Δ Costs, \$	2,753	4,527	4,656	5,329
Cost per life-year gained, \$	122,316	31,623	30,813	33,020
Cost per QALY gained, \$	144,235	37,467	36,508	39,112
Compared with next best strategy				
Δ Life-years	0.023	0.121	0.008	0.010
Δ QALY	0.019	0.102	0.007	0.009
Δ Costs, \$	2,753	1,774	129	672
Cost per life-year gained, \$	122,316	14,703	16,227	65,539
Cost per QALY gained, \$	144,235	17,436	19,242	77,319

NOTE. The baseline life-years gained, baseline QALYs, and baseline costs with standard of care are 0.167, 0.141, and \$3,905, respectively. Delta (Δ) life-years, QALY, and costs are the difference of each panel compared with the next best strategy or the standard of care. Panel 1 contains only Lynch-associated genes; panel 2 includes Lynch-associated genes plus those associated with autosomal dominant conditions and high colorectal cancer penetrance; panel 3 includes the genes in panel 2 plus the ones associated with autosomal recessive conditions and high colorectal cancer penetrance; and panel 4 includes the genes in panel 3 plus those associated with autosomal dominant conditions with low penetrance of colorectal cancer.

Abbreviation: QALY, quality-adjusted life-year.

Cost Effectiveness of NGS Panels in Inherited Colorectal Cancer

Fig 2. Tornado diagram of a one-way sensitivity analysis comparing panel 4 with standard of care. The model inputs at the top of the tornado diagram have the largest effect on the results. Only the top seven most influential parameters are represented. The x-axis scale is in dollars per quality-adjusted life-year (QALY). AD, autosomal dominant; CRC, colorectal cancer; CRCP, colorectal cancer and polyposis syndrome.

of panel testing seem to be modest per patient on average, this improvement is acceptable as a result of a relatively incremental cost per patient on average. Moreover, we found that the addition of genes associated with low-penetrance CRCP syndromes to the panel might also be cost effective, primarily because of the minimal additional cost of adding these genes to the NGS panel. The benefits of testing low-penetrance variants should be confirmed by further studies.

Our findings suggest that the use of NGS panels that include genes associated with highly penetrant CRCP syndromes can translate into better health outcomes and likely provide acceptable value to the health care system. For that reason, NGS panels that include these genes should be strongly considered as a first-line test for the evaluation of CRCP syndromes in patients referred to medical genetics clinics. Patients with pathogenic variants in non-Lynch syndrome

genes are not currently identified with the standard of care, unless their clinical presentation is suggestive of a single-gene condition. These individuals can have a clinical presentation indistinguishable from Lynch syndrome and, if a mutation in a non-Lynch syndrome gene is detected, may also benefit from early colonoscopy screening.¹³

To our knowledge, our study is the first modeling study of these clinical questions and suggests that NGS panels can be cost effective as an early step in the evaluation of a common inherited condition. Our study can help guide future investigation on the cost effectiveness of NGS panels for the evaluation of other hereditary cancers, such as breast cancer, and noncancer diseases, such as cardiomyopathies. Our findings also encourage evaluation of the cost effectiveness of more comprehensive uses of NGS applications, such as exome and genome sequencing, which are not currently indicated for common inherited adult-onset diseases.

We also conducted a scenario analysis to address the impact of universal Lynch syndrome screening programs in our referral population, and when compared with standard of care, this resulted in an ICER of \$39,300 per QALY using an NGS panel with genes associated with highly penetrant types of CRCP. In a population referred after universal Lynch syndrome screening, NGS panels would be cost effective because of their ability to detect non-Lynch syndrome pathogenic variants, as well as because of some benefit in identifying patients who are false negative for Lynch syndrome.

Although our analysis was not informed by data from a universal screening population, we did conduct an exploratory analysis to assess the value of NGS universal screening and found that when compared with universal standard of care testing, the use of NGS panels including genes associated with highly penetrant types of CRCP for universal screening of all patients with colorectal cancer would result in an ICER of \$70,600 per QALY. If the assumptions in this scenario analysis hold true and if stakeholders consider this ICER to be cost effective, then universal NGS CRCP screening in all patients with colorectal cancer should be considered. Importantly, data from NGS universal screening studies will be highly valuable for informing this policy decision.

Fig 3. Probabilistic sensitivity analyses of the incremental cost-effectiveness ratio of a comprehensive next-generation sequencing (NGS) panel including genes with highly penetrant syndromes (panel 3) versus standard of care in patients referred to the medical genetics clinic for evaluation of colorectal cancer and polyposis syndrome. Evaluation with NGS panel was cost effective in 74.6% of simulations if society is willing to pay \$50,000 per quality-adjusted life-year (QALY) and in 99% of simulations if society is willing to pay \$100,000 per QALY.

Our study has several key limitations. First, we assumed that the penetrance of disease in patients with pathogenic/likely pathogenic variants was similar to the penetrance of disease that is described in the literature for the associated conditions. If the penetrance of colorectal cancer in patients with pathogenic variants was in fact lower, this would lead to an overestimate of the cost effectiveness of NGS panels. Our one-way sensitivity analysis indicates that the disease penetrance of variants is an influential parameter but is not strong enough to change the conclusion on NGS panel cost effectiveness across a plausible range of values. In a threshold analysis, we estimated that the lifetime risk of developing colorectal cancer for individuals with highly penetrant CRCP syndromes would need to be 5% or lower for the cost effectiveness of an NGS panel compared with standard of care to be greater than the \$100,000 per QALY threshold.

A second limitation is the limited number of patients undergoing NGS panel evaluation as the basis of our model parameters on the distribution of pathogenic variants. We also evaluated this limitation using sensitivity analysis and found that uncertainty of the proportion of pathogenic/likely pathogenic variants was important, in particular for conditions with high colorectal cancer penetrance, but not enough to change our conclusions. Additional larger studies on the distribution of pathogenic variants with more patients are needed to confirm our estimates.

A third important limitation is the heterogeneous referral population seen in specialized cancer genetics clinics, because not all of the patients evaluated will have Lynch syndrome screening on tumor tissue as the first test and may instead have gene sequencing directly. To partially address the potential impact of this limitation, we assumed the most conservative cost estimates in the standard of care, meaning that our reference patient would start with immunohistochemistry, the cheapest test.

Finally, our study is limited by the assumptions we made in regard to the colorectal cancer similarities of Lynch syndrome to other types of CRCP syndromes, in particular similar cancer stage at diagnosis and expected benefits from intensive colonoscopy surveillance. We also assumed a similar age of onset of intensive screening and colonoscopy frequency across CRCP syndromes. Although there is some evidence suggesting that non-Lynch CRCP syndrome colorectal cancer might behave differently than Lynch syndrome colorectal can-

cer (eg, a more benign prognosis in the colorectal cancer associated with *MUTYH*-associated polyposis),³¹ the sensitivity analysis did not reveal a significant impact of variations in mortality rate with increased colonoscopy surveillance.

In summary, we evaluated the cost effectiveness of using various NGS panels for the evaluation of inherited colorectal cancer and polyposis syndromes in a cancer genetics clinic with the ultimate intent of preventing colon cancer in patients' relatives and found that if the conditions modeled here hold true in practice, the use of an NGS panel that includes genes associated with highly penetrant syndromes in addition to Lynch syndrome genes likely provides important clinical benefits and good value for the health care system. Additional studies are needed to determine whether these findings are applicable to other common phenotypes and to other, more comprehensive NGS applications, including universal NGS screening of all patients with colorectal cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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GLOSSARY TERMS

Cost-effectiveness analysis: an economic evaluation in which the costs and consequences of alternative interventions are expressed as a cost per unit of health outcome. Cost-effectiveness analysis is used to determine technical efficiency (ie, comparison of costs and consequences of competing interventions for a given patient group within a given budget).

Penetrance: the likelihood that a given gene mutation will produce disease. This likelihood is calculated by examining the proportion of people with the particular genetic mutation that show symptoms of disease.

Proband: the likelihood that a given gene mutation will produce disease. This likelihood is calculated by examining the proportion of people with the particular genetic mutation that show symptoms of disease.

Quality-adjusted life-year (QALY): a common measure of health improvement used in economic evaluation that measures life expectancy adjusted for quality of life.

Sensitivity analysis: analyses that evaluate the impact of missing data and possible differences in interval assessments.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Next-Generation Sequencing Panels for the Diagnosis of Colorectal Cancer and Polyposis Syndromes: A Cost-Effectiveness Analysis**

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or jco.ascopubs.org/site/ifc.

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No relationship to disclose

Brian H. Shirts

Consulting or Advisory Role: Avalon Healthcare Solutions

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No relationship to disclose

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No relationship to disclose

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Patents, Royalties, Other Intellectual Property: Methylation-specific polymerase chain reaction assay for *MLH1*

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Consulting or Advisory Role: Genentech, Abbott Diabetes, Jazz Pharmaceuticals

Travel, Accommodations, Expenses: Genentech

Acknowledgment

We thank Mercy Mvundura, PhD, and Scott D. Grosse, PhD, for developing and sharing the Centers for Disease Control and Prevention economic model of universal screening for Lynch syndrome in patients with colorectal cancer. This work would not have been possible without their input.

Appendix

Model Inputs

Clinical data. The probabilities of having colorectal cancer and polyposis (CRCP)–related pathogenic variants were estimated from the next-generation sequencing (NGS) panel database at the Department of Laboratory Medicine at the University of Washington.²⁰ A quality assurance specialist reviewed the samples sent for evaluation by an NGS panel (ColoSeq) specific for patients with suspected hereditary CRCP syndromes. The ColoSeq panel reads all intronic and exonic sequences of 19 genes associated with hereditary CRCP (Appendix Table A5). Patients were referred to NGS testing based on a variety of factors, including clinical presentation and family history, but not likely specific criteria such as the Amsterdam criteria. The patient's clinical history was obtained from genetic counselors at the time of referral and was used to exclude noneligible patients. Excluded patients included minors, patients with a pathogenic variant already identified in their family, and patients with a clinical presentation consistent with having a pathogenic variant in a single gene. We also excluded patients with more than 20 polyps because arguably these individuals should be sequenced for the *MUTYH* and/or *APC* genes only.^{16,17} All procedures were approved by the Institutional Review Board of University of Washington.

Relatives per proband. The average number of relatives per proband and the proportion of relatives accepting counseling and accepting testing were obtained from the Supplementary Evidence Review performed as part of the Evaluation of Genomic Applications in Practice and Prevention pilot program for Lynch syndrome.²⁷

Laboratory data. Data on sensitivity and specificity of immunohistochemistry and sequencing/multiplex ligation-dependent probe amplification were obtained from the Evaluation of Genomic Applications in Practice and Prevention Supplementary Evidence Review (Evaluation of Genomic Applications in Practice Prevention Working Group: Genet Med 11:35-41, 2009) and a recent systematic review.²² Data on sensitivity and specificity of NGS panels were obtained from the Laboratory Medicine Department at the University of Washington.²⁶

Impact on relatives. The outcomes and costs per pathogenic variant identified in a relative were obtained from a cost-effectiveness model developed by the Centers for Disease Control and Prevention¹⁹ 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 the literature (Neklason DW, et al: Clin Gastroenterol Hepatol 6:46-52, 2008; Wong P, et al: Gastroenterology 130:73-79, 2006; Tan MH, et al: Clin Cancer Res 18:400-407, 2012; Hearle N, et al: Clin Cancer Res 12:3209-3215, 2006; Sampson JR, et al: Lancet 362:39-41, 2003; Howe JR, et al: Science 280:1086-1088, 1998; Lubbe SJ, et al: J Clin Oncol 27:3975-3980, 2009)^{13,28} and by consensus from a multidisciplinary group of medical geneticists and gastroenterologists (C.J.G., F.M.H., W.M.G., G.P.J.). The Centers for Disease Control and Prevention model was originally developed for outcomes in Lynch syndrome patients, and we assumed a similar stage distribution of colorectal cancer at the time of diagnosis as well as a similar relative survival rate in non-Lynch CRCP syndromes. The risk reduction in colorectal cancer for patients undergoing intensive colonoscopy surveillance in non-Lynch syndrome patients was assumed to be 62%, the same estimate for Lynch syndrome patients (Evaluation of Genomic Applications in Practice Prevention Working Group: Genet Med 11:35-41, 2009).

Cost data. The costs of genetic services were obtained from previous literature and a team of genetic counselors at the University of Washington. The costs of testing were estimated from the billing services of the Department of Laboratory Medicine. Data obtained from previous literature were adjusted for inflation using the consumer price index and updated to reflect 2014 costs (Gould-Suarez M, et al: Dig Dis Sci 59:2913-2926, 2014; Dinh TA, et al: Cancer Prev Res 4:9-22, 2011).^{19,22-25}

Table A1. Distribution of Pathogenic and Likely Pathogenic Variants in Individuals Tested for Suspected CRCP Syndromes With NGS Panels at the University of Washington Molecular Genetics Laboratory, According to Type of Inheritance and Penetrance of Colorectal Cancer of Associated CRCP Syndrome

Variants by CRCP Syndrome Type	No. of Individuals
Lynch associated	30
Autosomal dominant CRCP with high colorectal cancer penetrance	13
Autosomal recessive CRCP with high colorectal cancer penetrance	4
Autosomal dominant CRCP with low colorectal cancer penetrance	7
No CRCP-associated variant identified	297

Abbreviations: CRCP, colorectal cancer and polyposis syndromes; NGS, next-generation sequencing.

Table A2. Incremental Cost-Effectiveness Ratio and Differences in Payoffs in a Scenario Analysis Where Only First-Degree Relatives Are Approached, Comparing Each Hypothetical Panel With Standard of Care or the Next Most Effective Strategy

Measure	Panel 1	Panel 2	Panel 3	Panel 4
Compared with standard of care				
Δ Life-years	0.010	0.061	0.066	0.070
Δ QALY	0.008	0.052	0.055	0.059
Δ Costs, \$	2,494	3,241	3,308	3,589
Cost per life-year gained, \$	260,630	52,891	50,353	51,204
Cost per QALY gained, \$	307,322	62,665	59,661	60,653
Compared with next best strategy				
Δ Life-years	0.010	0.052	0.004	0.004
Δ QALY	0.008	0.044	0.004	0.004
Δ Costs, \$	2,494	747	67	281
Cost per life-year gained, \$	260,630	14,449	15,160	63,928
Cost per QALY gained, \$	307,322	17,134	17,977	75,418

NOTE. The baseline life-years gained, baseline QALYs, and baseline costs with standard of care are 0.072, 0.061, and \$2,047, respectively. Delta (Δ) life-years, QALY, and costs are the difference of each panel compared with the next best strategy or the standard of care. Panel 1 contains only Lynch-associated genes; panel 2 includes Lynch-associated genes plus those associated with autosomal dominant conditions and high colorectal cancer penetrance; panel 3 includes the genes in panel 2 plus the ones associated with autosomal recessive conditions and high colorectal cancer penetrance; and panel 4 includes the genes in panel 3 plus those associated with autosomal dominant conditions with low penetrance of colorectal cancer.

Abbreviation: QALY, quality-adjusted life-year.

Table A3. Incremental Cost-Effectiveness Ratio and Differences in Payoffs in a Scenario Analysis to Evaluate the Impact of Lynch Syndrome Universal Screening Programs in Our Referral Population

Measure	Panel 1	Panel 2	Panel 3	Panel 4
Compared with standard of care				
Δ Life-years	0.032	0.153	0.161	0.171
Δ QALY	0.027	0.129	0.136	0.144
Δ Costs, \$	3,432	5,206	5,335	6,007
Cost per life-year gained, \$	106,714	34,066	33,183	35,124
Cost per QALY gained, \$	126,050	40,363	39,319	41,607
Compared with next best strategy				
Δ Life-years	0.032	0.121	0.008	0.010
Δ QALY	0.027	0.102	0.007	0.009
Δ Costs, \$	3,432	1,774	129	672
Cost per life-year gained, \$	106,714	14,703	16,227	65,539
Cost per QALY gained, \$	126,050	17,436	19,242	77,319

NOTE. There are no baseline life-years or QALYs gained with standard of care, and the cost per patient is \$199, the cost of the clinic visit. Delta (Δ) life-years, QALY, and costs are the difference of each panel compared with the next best strategy or the standard of care. Panel 1 contains only Lynch-associated genes; panel 2 includes Lynch-associated genes plus those associated with autosomal dominant conditions and high colorectal cancer penetrance; panel 3 includes the genes in panel 2 plus the ones associated with autosomal recessive conditions and high colorectal cancer penetrance; and panel 4 includes the genes in panel 3 plus those associated with autosomal dominant conditions with low penetrance of colorectal cancer.

Abbreviation: QALY, quality-adjusted life-year.

Cost Effectiveness of NGS Panels in Inherited Colorectal Cancer

Table A4. Incremental Cost-Effectiveness Ratio and Differences in Payoffs in a Scenario Analysis to Evaluate the Cost Effectiveness of NGS Panels As a Universal Screening Test on All Patients Diagnosed With Colorectal Cancer

Measure	Panel 1	Panel 2	Panel 3	Panel 4
Compared with standard of care				
Δ Life-years	0.008	0.050	0.053	0.057
Δ QALY	0.007	0.042	0.045	0.048
Δ Costs, \$	2,492	3,115	3,160	3,396
Cost per life-year gained, \$	315,390	61,981	59,572	59,952
Cost per QALY gained, \$	371,908	73,434	70,584	71,013
Compared with next best strategy				
Δ Life-years	0.008	0.042	0.003	0.004
Δ QALY	0.007	0.036	0.002	0.003
Δ Costs, \$	2,492	623	45	236
Cost per life-year gained, \$	315,390	14,703	16,227	65,539
Cost per QALY gained, \$	371,908	17,436	19,242	77,319

NOTE. The baseline life-years gained, baseline QALYs, and baseline costs with standard of care are 0.058, 0.050, and \$1,799, respectively. Delta (Δ) life-years, QALY, and costs are the difference of each panel compared with the next best strategy or the standard of care. Panel 1 contains only Lynch-associated genes; panel 2 includes Lynch-associated genes plus those associated with autosomal dominant conditions and high colorectal cancer penetrance; panel 3 includes the genes in panel 2 plus the ones associated with autosomal recessive conditions and high colorectal cancer penetrance; and panel 4 includes the genes in panel 3 plus those associated with autosomal dominant conditions with low penetrance of colorectal cancer. Abbreviations: NGS, next-generation sequencing; QALY, quality-adjusted life-year.

Table A5. List of CRCP Syndromes and Associated Genes Tested by NGS Panel (ColoSeq) at the Department of Laboratory Medicine at University of Washington

Disease Name or Cancer Risk	Associated Gene
Lynch syndrome, Muir-Torre syndrome	<i>MLH1, MSH2</i>
Lynch syndrome	<i>PMS2, MSH6, EPCAM</i>
Attenuated familial adenomatous polyposis, Turcot's syndrome	<i>APC</i>
<i>MUTYH</i> -associated polyposis	<i>MUTYH</i>
Juvenile adenomatous polyposis	<i>BMPR1A, SMAD4</i>
Cowden's syndrome	<i>PTEN</i>
Hereditary diffuse gastric cancer	<i>CDH1</i>
Li-Fraumeni syndrome	<i>TP53</i>
Colon cancer	<i>GALNT12</i>
Peutz-Jeghers syndrome	<i>STK11</i>
Colon cancer, endometrial cancer	<i>POLE</i>
Colon cancer	<i>POLD1</i>
Polyposis	<i>GREM1</i>
Breast cancer, thyroid cancers, macrocephaly	<i>AKT1</i>
Breast cancer, thyroid cancers, macrocephaly	<i>PIK3CA</i>

Abbreviations: CRCP, colorectal cancer and polyposis syndromes; NGS, next-generation sequencing.