

Color's Hereditary Cancer Genetic Testing

Actionable Insights to Inform Risk-Based Disease Management

Version 1 - Updated 10.5.2026

Executive Summary

Color's Hereditary Cancer Genetic Test is built on a validated next-generation sequencing (NGS) platform and analyzes 29 genes associated with the most common hereditary cancer risk syndromes represented across National Comprehensive Cancer Network (NCCN) hereditary cancer guidelines. The test enables healthcare providers to identify individuals with inherited cancer risk, personalize screening plans, offer risk-reducing interventions, and make more informed treatment decisions.

Color's assay deeply sequences targeted regions and uses a suite of highly refined bioinformatic tools to detect a broad range of genetic variants, including single nucleotide variants, small insertions and deletions, and copy number variants. Specialized methods are used to address technically challenging regions and complex variant types. Color's clinical interpretation teams apply rigorous, evidence-based processes to variant classification and reporting, helping ensure results are accurate, clear, and clinically useful.

Color's testing is used by employers, health systems, research institutions, and public health programs to provide scalable access to high-quality genetic testing and support both individual patient care and population health initiatives. Within the Color Virtual Cancer Clinic, hereditary cancer genetic testing is integrated into criteria-based testing programs informed by NCCN guidelines to identify individuals with inherited cancer risk and connect them with appropriate screening, prevention, and ongoing care.

Introduction

Advancements in genomic sequencing have transformed how we detect, manage, and prevent disease. Once prohibitively expensive and time-consuming, clinical-grade genetic testing is now accessible and increasingly embedded in routine care. Color's genetic testing platform brings this technology into cancer prevention and care, with a focus on identifying high-impact, actionable variants linked to well-established clinical protocols.¹⁻⁴

Color's Hereditary Cancer Genetic Test analyzes 29 genes associated with risk for breast, ovarian, colorectal, melanoma, pancreatic, prostate, stomach, and uterine cancers.^{1,3} The test focuses on genes with established associations with hereditary cancer risk and potential implications for cancer care, including hereditary breast and ovarian cancer, Lynch syndrome, and hereditary polyposis syndromes. Identifying a pathogenic or likely pathogenic variant can help individuals and their healthcare providers better understand cancer risk and, when appropriate, inform personalized screening and risk-reducing strategies.⁵⁻⁸

Test Overview

Color's Hereditary Cancer Genetic Test uses next-generation sequencing (NGS) to detect a broad range of clinically relevant variant types, including single nucleotide variants (SNVs), small insertions and deletions (indels), and larger deletions and duplications (copy number variants, or CNVs). Specialized methods are used to detect certain technically challenging variants and analyze regions where standard sequencing approaches may be insufficient.

The majority of genes are analyzed across all coding exons and flanking intronic regions, with targeted analysis used for genes or regions where specific variants are associated with cancer risk. Detailed information about the genes and regions analyzed is provided in the Appendix.

 Validated Color performed blinded validation studies to assess the validity of our genetic tests, and all genetic variants were detected with >99% sensitivity and 100% concordance. To read our technical validation papers, peer-reviewed publications, and research posters, visit our Research page.	 Quality-checked The quality of every sample is checked multiple times as it moves through the sequencing process and as the data is interpreted. A board-certified medical geneticist or pathologist reviews every result before it is released.	 State-of-the-art variant classification Color's infrastructure provides our team the ability to work quickly and efficiently as they classify variants according to the American College of Medical Genetics and Genomics (ACMG guidelines), and integrate new data to re-evaluate variants over time.	 Secondary confirmations Likely pathogenic and pathogenic variants, including single nucleotide variants, insertions and deletions, and structural variants, are confirmed by an alternative technology according to Color's internal protocols.*
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Sequencing Technology & Methodology

Color's Hereditary Cancer Genetic test is built on a robust, clinical-grade next-generation sequencing (NGS) platform, optimized for accuracy and scalability. All testing is performed in a CLIA-certified (05D2081492) and CAP-accredited (8975161) laboratory using validated protocols and automated quality control checks at each stage.⁸⁻¹⁰

Sample Collection and DNA Processing

DNA is extracted from validated sample types, including saliva and blood, using automated extraction protocols. DNA quality and quantity are assessed using spectrophotometric and fluorometric methods to ensure sufficient input for library preparation. For most assays, high molecular weight genomic DNA is enzymatically fragmented and prepared for sequencing using the KAPA HyperPlus Library Prep Kit (Roche/Kapa Biosciences), automated on Hamilton STAR systems.¹⁰

Target Enrichment and Sequencing

Targeted enrichment is performed using Agilent's SureSelect capture probes designed for the reportable regions of the Hereditary Cancer Genetic Test to target the complete coding regions of selected genes, with inclusion of intron-exon boundaries (typically -15/+6bp) and additional non-coding regions known to harbor clinically relevant variants (e.g., deep intronic *MSH2* splice variants and regulatory *GREM1* regions).¹¹⁻¹³

Sequencing is performed using Illumina's NovaSeq 6000 platform, with 150 bp paired-end reads and high-depth coverage across all target regions. Each run includes two fully characterized positive control samples (e.g., NA12878 and NA19240) and a no-template control to ensure run integrity.

Bioinformatics Pipeline

Color's custom bioinformatics pipeline uses industry-standard algorithms:

- Alignment: BWA-MEM against GRCh37 (hg19)¹⁵
- Variant Calling: GATK, DeepVariant, and proprietary algorithm for homopolymer regions (using BCFtools)¹⁶⁻¹⁷
- Structural Variant Detection: CNVkit (read depth), Dysgu (paired/split reads), and proprietary algorithms (including mobile element insertions)^{13, 18}
- Genotyping: challenging variants across all variant types using patented algorithm
- Specialized analysis: dedicated methods are used for technically challenging genomic regions and variant types

For example, analysis of *PMS2* exons 12–15 requires specialized methods to distinguish variants in *PMS2* from variants in its highly homologous pseudogene, *PMS2CL*. Candidate variants in these regions are localized using long-range PCR followed by nested PCR and Sanger sequencing.

The pipeline includes rigorous quality-control checkpoints throughout analysis and is designed to generate high-confidence variant calls for single nucleotide variants (SNVs), small insertions and deletions (indels), copy number variants (CNVs), and select structural rearrangements (e.g., inversions, mobile element insertions).

Coverage and Performance

At least 99.5% of regions in the reportable range meet or exceed 20x coverage. Median depth typically ranges from 200x to 300x, with high uniformity across targets. Regions that consistently fall below quality thresholds are excluded from analysis and documented in the test description.

Performance metrics such as accuracy, sensitivity, specificity, reproducibility, and repeatability have been validated.

Interpretation Framework

Color's interpretation framework is built to ensure that every reported variant meets high standards of analytical validity, clinical relevance, and transparency. Our approach combines automated data analysis with expert review to support high-confidence, clinically actionable results.

Variant Classification

All variants are classified using the American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) guidelines for sequence variant interpretation.⁸ Variants are assigned to one of five categories:

- Pathogenic
- Likely pathogenic
- Variant of uncertain significance (VUS)
- Likely benign
- Benign

Classification is based on multiple lines of evidence, including population frequency, computational predictions, functional data, segregation studies, and disease-specific case data.²¹⁻²⁴ Color incorporates allele frequency and variant annotation data from a range of public and internal sources, including gnomAD²¹, ClinVar²², BRCA Exchange²³, and other relevant resources. Computational prediction tools, conservation metrics, and disease-specific variant evidence are used in line with ACMG/AMP guidelines.^{8,24} Each classification is documented and tracked for consistency and transparency.

Expert Review and Curation

All clinically significant variants (pathogenic and likely pathogenic) undergo detailed review by Color's team of certified clinical geneticists and variant scientists. Reportable findings are evaluated by a board-certified medical geneticist or pathologist. Color's curation team monitors emerging evidence and may update variant classifications as new evidence becomes available, helping ensure classifications reflect the current understanding of the relationship between genetic variation and disease.²⁵

Variant Confirmation

Variant calls with potential clinical impact may be confirmed using orthogonal methods, such as Sanger sequencing, MLPA, aCGH or variant-specific PCR, particularly for challenging regions and/or variant types. This step supports confidence in results before clinical reporting and aligns with best practices in molecular diagnostics.⁹

Limitations

While Color's Hereditary Cancer Genetic Test is highly sensitive and analytically validated, certain limitations are inherent to the technology, assay design, and current state of genomic knowledge. These limitations are important to consider in the clinical interpretation of results.

Technical Limitations

The Hereditary Cancer Genetic Test is designed to detect single nucleotide variants (SNVs), small insertions and deletions (indels), copy number variants (CNVs), and select structural variants within the test's reportable regions. Certain types of genetic variation may not be detected, including balanced rearrangements, repeat expansions, epigenetic changes, and variants located outside the regions targeted by the assay. Detection of mosaic variants may be limited when the variant is present at a low allele fraction.

Certain genomic regions are technically challenging to analyze because of factors such as high GC content, repetitive sequence, or homology with pseudogenes. Color uses specialized methods to address known challenging regions, including *PMS2* exons 12–15, but some rare or complex variants may remain difficult to detect or definitively localize.¹⁹

The majority of genes are analyzed across coding exons and flanking intronic regions; however, analysis of certain genes is intentionally limited to specific regions or variant types with established associations with cancer risk. Detailed reportable ranges and gene-specific limitations are provided in the test description.

Interpretive Limitations

The Hereditary Cancer Genetic Test is a targeted gene panel and does not evaluate all genes associated with inherited cancer risk. A negative result therefore does not eliminate the possibility of an inherited predisposition to cancer, including risk associated with genes or genomic regions not included in the test.

Some variants cannot be definitively classified as pathogenic or benign based on currently available evidence and are classified as variants of uncertain significance (VUS). VUS findings should not be used independently to guide clinical management. Variant classifications reflect the evidence available at the time of interpretation and may change as new information becomes available.

Importantly, genetic test results represent one component of an individual's overall cancer risk assessment. Personal and family history and other clinical risk factors should also be considered when determining appropriate cancer screening and risk-reduction strategies.^{8,25}

Validation Data

Hereditary Cancer Genetic Test

Our validation strategy adhered to guidelines for NGS from the College of American Pathologists (CAP), the ACMG,¹² the Clinical and Laboratory Standards Institute,²⁶ the Nex-StoCT workgroup for Standardization of Clinical Testing by NGS²⁷ and FDA Standards for NGS.²⁸ The validation study included saliva samples, well-characterized cell lines and DNA specimens, previously extracted from blood from patients who had been diagnosed with hereditary

cancer and whose genetic variants had been previously characterized elsewhere (Table 1). Together these groups constitute a good representation of the possible variant types across the genes in Color’s Hereditary Genetic Tests.

Study 1: Reference materials with public data

Every sequencing run contains two positive controls (NA12878 and NA19240), which have been recommended as reference materials by the National Institute of Standards and Technology (NIST).¹⁴ In addition, Color has sequenced the Ashkenazi Jewish father-mother-son trio NA24149, NA24143 and NA24385. Variant calls in these reference materials were compared against the union of reported variants by NIST [NCBI Get-RM] and Complete Genomics.^{29,30} Several low-confidence variants in the NIST and Complete Genomics datasets were confirmed by Sanger sequencing at an independent laboratory.

Specimen	Number of non-pathogenic variants			Total
	SNVs	Indels	CNVs	
NA12878	60	4	0	64
NA19240	55	4	0	59
NA24143	46	2	0	48
NA24149	55	3	0	58
NA24385	54	2	0	56
Total	270	15	0	285

Table 1a. Study 1. Overview of variants, stratified by variant type. NIST reference materials.⁵⁰

Study 2: Blinded specimens from patients with personal history of cancer

The hereditary genetics assay and tests were validated in part using two groups of patients who had previously been diagnosed with cancer. The first group consisted of 29 cell lines (Coriell Institute for Medical Research and American Type Culture Collection (ATCC)), many of which carry pathogenic variants in BRCA1 and BRCA2. The second group consisted of 507 anonymized DNA specimens provided by Mary-Claire King, Ph.D. and Tom Walsh, Ph.D. Of these 507 specimens, 183 specimens had pathogenic variants previously identified in at least one of 30 genes,^{3,31-40} and the other 324 specimens had tested negative for germline variants in the same genes. Importantly, these clinical samples were provided to Color in a “blinded” manner; i.e. Color did not have information regarding the status or genetic makeup of the samples other than the past cancer history. After the Color test was performed, results were submitted to our collaborators to be compared against the previously identified variants. This allowed Color to test the accuracy of its assay in the absence of any a priori knowledge of genetic variants.

Specimen	Number of pathogenic variants			Number of likely pathogenic variants			Total
	SNVs	Indels	CNVs	SNVs	Indels	CNVs	
Cell lines (n=29)	14	18	NA	4	1	NA	37
Clinical samples, blinded group (n=507)	65	69	43	16	1	6	200
Total	79	87	43	20	2	6	237

Table 1b. Study 2. Overview of pathogenic and likely pathogenic variants, stratified by variant type: 29 cell lines [Coriell Institute and American Type Culture Collection] and 507 clinical samples.

Study 3: Independent confirmation of variants in consecutive Color cohort

As part of Color's quality control system, a set of 640 variants was submitted for confirmation by Sanger sequencing. This set contains 206 variants, detected in the initial consecutive cohort of Color's 19-gene breast and ovarian cancer genetic test, that had been classified as pathogenic or likely pathogenic.

Study 4: Technical precision: reproducibility and repeatability

Precision of the Color Genetic Tests is assessed with 3 replicate runs, which were performed by different operators. These runs used multiple lot numbers of critical reagents such as DNA polymerase and baits as well as multiple thermo-cyclers and sequencers. Intra-assay repeatability was computed by comparing results for 22 unique samples that had been replicated multiple times within the same run. Inter-assay reproducibility was assessed by comparing results for 61 unique samples that had been replicated multiple times across different runs. These precision measurements were calculated using all detected variants, independent of variant type (SNV/indel/CNV), classification and confirmation.

Study	Specimen	Number of variants	True Positives	False Positive*	False Negative*
1	NA12878	64	64	0	0
	NA19240	59	59	0	0
	NA24143	48	48	0	0
	NA24149	58	58	0	0
	NA24385	56	56	0	0
2	Coriell/ATCC cell lines (n=29)	37	37	0	0
2	Blinded samples (n=507)	200	200	0	0
Total	541	522	522	0	0

Table 2. Studies 1-2. Assessment of accuracy in detection of rare single nucleotide variants, insertions/deletions and copy number variants.

**Assessment of False Positives and False Negatives was based on all variants in the reportable range for the recommended NIST reference materials (Table 1a) and all (likely) pathogenic variants in the remaining validation specimens.*

Results

The Color Genetic Tests have proven analytical validity and 100% concordance with known, evaluated variants across 507 previously sequenced clinical samples and 34 cell lines. The 522 variants identified in previous clinical testing, including SNVs, small indels, and CNVs, were correctly detected in a blinded analysis. In this dataset, 237 variants had been classified as pathogenic or likely pathogenic, while no false positive pathogenic variants were

called in any of these 541 samples (Table 2). In addition, all 640 germline variants submitted for Sanger sequencing were confirmed and no additional variants of relevance were detected (Table 3).

Gene	Total	True Positives	False Positives	False Negatives
ATM	94	94	0	0
BARD1	29	29	0	0
BRCA1	48	48	0	0
BRCA2	85	85	0	0
BRIP1	38	38	0	0
CDH1	23	23	0	0
CHEK2	77	77	0	0
MLH1	21	21	0	0
MSH2	52	52	0	0
MSH6	50	50	0	0
PALB2	32	32	0	0
PMS2	24	24	0	0
PTEN	2	2	0	0
RAD51C	13	13	0	0
RAD51D	11	11	0	0
STK11	8	8	0	0
TP53	9	9	0	0
Total	616	616	0	0
NBN*	24	24	0	0

Table 3. Study 3. Overview of secondary confirmation results by Sanger sequencing for 640 variants, of which 206 variants had been classified as likely pathogenic or pathogenic in a consecutive cohort of patients taking the Color 19-gene genetic test for breast and ovarian cancer.

*NBN was removed from the panel in 2022

Repeatability within-run amounted to 100% over 1212 variants (Jeffreys 95% Confidence Interval: 0.998-1), while reproducibility between-runs was 9613 of 9615 variants (99.98%, 95% CI: 0.999-1, see Table 4).

	Studies	Results	Score [Jeffreys 95% CI]
Accuracy	1-2	541/541 samples	100% [0.995-1]
Sensitivity	1-2	522/522 variants	100% [0.995-1]

Specificity PPV*	1-2 1-3	0 FPs** in 541 samples 0 FPs** in 522+640=1162 variants	100% [0.995-1] 100% [0.998-1]
Repeatability Reproducibility	4 4	1212/1212 variants 9613/9615 variants***	100% [0.998-1] 99.98% [0.999-1]

Table 4. Overview of Color Test performance across validation studies 1-4. *PPV = Positive Predictive Value. **FP = False Positive. ***Two likely benign variants, located in a homopolymer repeat and in a region of high GC content, were not reproduced in all replicates.

Conclusion

Color’s Hereditary Cancer Genetic Test provides clinically relevant genetic information to help identify individuals with inherited cancer risk and inform personalized approaches to cancer screening, prevention, treatment, and care.

Built on a validated next-generation sequencing platform, the test analyzes 29 hereditary cancer genes and is designed to detect a broad range of variant types, including single nucleotide variants, small insertions and deletions, copy number variants, and select structural variants. Color combines rigorous laboratory and bioinformatics methods with evidence-based variant classification and expert clinical review to support accurate and reliable results. Validation of the assay demonstrated 100% accuracy for 522 variants representing SNVs, indels, and CNVs in the validation dataset.

By integrating high-quality genetic testing into clinical and population health programs, Color supports scalable identification of individuals with inherited cancer risk and helps connect genetic insights with appropriate clinical care. This approach enables genetic testing to support both individual risk assessment and broader efforts to improve cancer prevention and early detection.

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Supplement

Supplemental Table 1. Known associations between genes in Color’s Hereditary Cancer Genetic Tests and cancer type.

Gene	Breast	Ovarian	Uterine	Colorectal	Melanoma	Pancreatic	Stomach	Prostate
BRCA1	•	•				•		•
BRCA2	•	•			•	•		•
MLH1		•	•	•		•	•	•
MSH2		•	•	•		•	•	•
MSH6		•	•	•			•	•
PMS2		•	•	•				•
EPCAM [†]		•	•	•		•	•	•
APC				•		•	•	
MUTYH [†]				•				
MITF [†]					•			
BAP1					•			
CDKN2A					•	•		
CDK4 [†]					•			
TP53	•	•	•	•	•	•	•	•
PTEN	•		•	•	•			
STK11	•	•	•	•		•	•	
CDH1	•						•	
BMPR1A				•			•	
SMAD4 [†]				•			•	
GREM1 [†]				•				
POLD1 [†]				•				
POLE [†]				•				
PALB2	•	•				•		
CHEK2	•			•				•
ATM	•					•		
BARD1	•							
BRIP1	•	•						
RAD51C	•	•						
RAD51D	•	•						

[†] Analysis limited to positions known to impact cancer risk (genomic coordinates in GRCh37): in CDK4, only chr12:g.58145429-58145431 (codon 24); in EPCAM, only large deletions and duplications including 3' end of the gene; in GREM1, only duplications in the upstream regulatory region; in MITF, only chr3:g.70014091 (including c.952G>A); in MUTYH, only biallelic or at least two (likely) pathogenic variants in unknown phase; in *PMS2*: variants of uncertain significance are not reported for exons 12-15. Analysis excludes five variants commonly observed in the pseudogene *PMS2CL*: c.2182_2184delinsG, c.2243_2246del, c.2444_2445insTT, c.2523G>A, and deletion of exons 13-14 (chr7:g.6015768_6018727del). In POLD1, only chr19:g.50909713 (including c.1433G>A); in POLE, only chr12:g.133250250 (including c.1270C>G). SMAD4: Presence of the processed pseudogene may impact the ability to call structural variants in SMAD4.