Testing for CDC Tier 1 genomic conditions

The CDC has recognized the significant public health impact of identifying people with Tier 1 genomic conditions[1]: Hereditary Breast and Ovarian Cancer, Lynch Syndrome, and Familial Hypercholesterolemia. Yet, it's estimated that 90% of affected individuals are unaware of their risk[2-5].

"Nearly 2 million people in the United States are at increased risk for adverse health outcomes because they have genetic mutations which predispose them to one of the following conditions:

- *Hereditary Breast and Ovarian Cancer Syndrome (HBOC)*: increased risk for breast, ovarian, tubal, peritoneal, and other cancers due to mutations in *BRCA1* or *BRCA2* genes;
- *Lynch Syndrome (LS):* increased risk for colorectal, endometrial, ovarian, and other cancers associated with mutations in mismatch-repair genes; or
- *Familial Hypercholesterolemia (FH):* increased risk for heart disease or stroke due to mutations leading to very high cholesterol levels from an early age

Because, at present, these conditions are poorly ascertained by the healthcare system, many individuals and families affected by them are not aware that they are at risk; however, early detection and intervention could significantly reduce morbidity and mortality."

Source: CDC. Tier 1 Genomics Applications and their Importance to Public Health. Accessed May 2018.

Color's testing for CDC Tier 1 genomic conditions

Color's testing for CDC Tier 1 genomic conditions includes a physician-ordered genetic test and access to genetic counselors for no additional cost. The test analyzes 10 genes in which mutations are associated with an elevated risk of Hereditary Breast and Ovarian Cancer Syndrome, Lynch Syndrome, and Familial Hypercholesterolemia: *BRCA1, BRCA2, APOB, LDLR, PCSK9, MLH1, MSH2, MSH6, PMS2, EPCAM*.

Color's platform also includes patient recruitment, provider education, pedigree collection, cascade screening, and ongoing updates as screening guidelines, risk information, or variant classifications change.

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How Color works: the patient experience

Provide sample

A physician-ordered Color test kit is purchased online and shipped to the patient's home. The saliva sample is placed in the tube provided and shipped back to Color.

Review results

Patient receives their detailed risk assessment report online. Every result is reviewed by a certified medical professional before it is released and takes into account the patient's provided personal and family health history.

Access genetic counselors

Patient discusses results and questions with a board-certified, licensed genetic counselor from Color (or from your health system's genetic counselors).

Create a plan

Color shares test results with the patient's healthcare providers to help develop individualized screening and prevention plans.

Receive ongoing support

Color includes complimentary updates when information about the patient's risk or screening guidelines change, personal or family health histories change, or when new genes impact risk for diseases Color has already reported on.

How is testing for CDC Tier 1 genomic conditions actionable?

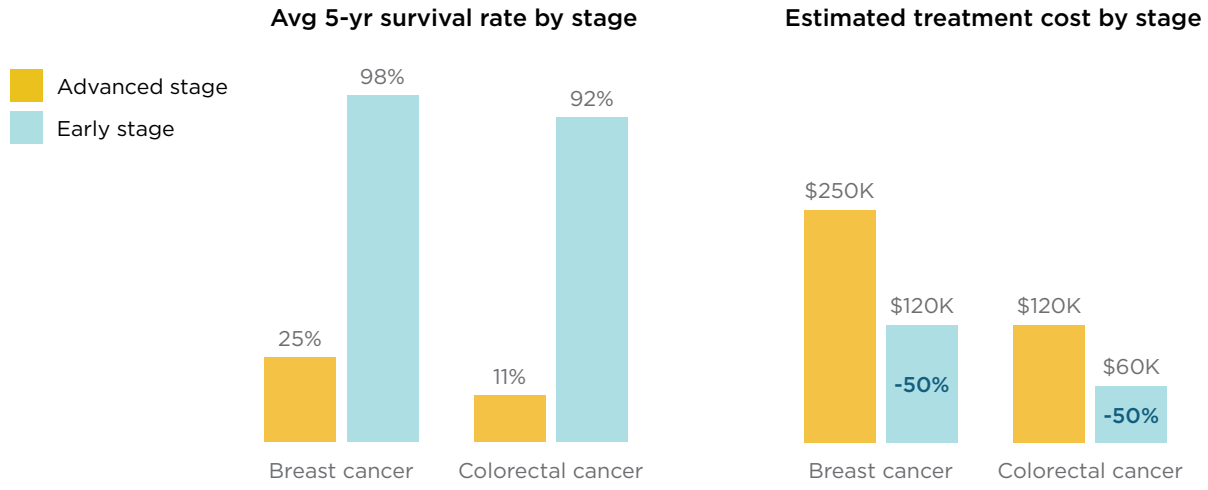
If your patients learn they have a mutation that increases their risk for a hereditary condition, they can work with their healthcare provider to create a personalized screening and risk management plan designed to prevent or detect conditions at an earlier or more treatable stage.

- ***Hereditary Breast and Ovarian Cancer Syndrome (HBOC):*** Apply National Comprehensive Cancer Network (NCCN) guidelines, including mammographies, MRI, physical exams, and potentially pelvic ultrasounds, CA-125 blood tests, or risk-reducing surgeries.
- ***Lynch Syndrome (LS):*** Apply NCCN guidelines, including colonoscopies, endoscopies, transvaginal ultrasounds, endometrial biopsy, and potentially risk-reducing surgeries.
- ***Familial Hypercholesterolemia (FH):*** Monitor cholesterol and undergo pharmacologic treatment and lifestyle interventions.

Testing for CDC Tier 1 genomic conditions

Earlier detection improves survival rates and reduces treatment costs

Studies indicate meaningful improvements in 5-year survival rates (the percentage of patients still alive 5 years after diagnosis) and reductions in treatment costs when cancer is caught in its early versus advanced stage.



Sources: Survival rates from National Cancer Institute; Inflation-adj treatment costs from American Health & Drug Benefits (breast), Journal of the National Cancer Institute and Health Care Financing Review (colorectal)

Analytical validity

Cancer

- Color's Hereditary Cancer Test detected genetic variants with greater than 99% accuracy
- 100% concordance in 507 previously sequenced clinical samples and 34 cell lines
- Repeatability 100% over 1212 variants (Jeffreys 95% Confidence Interval: 0.998-1)
- Reproducibility 99.98%, 95% CI: 0.999-1
- Full Hereditary Cancer Genetic Test Validation study available at color.com/whitepaper
- CAP #8975161, CLIA #05D2081492, CE Marked, NYSDOH approved

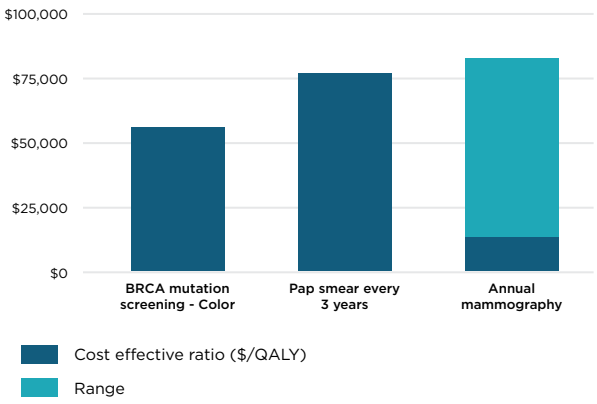
Familial Hypercholesterolemia

- Color's Hereditary High Cholesterol Test detected genetic variants with greater than 99% accuracy
- 100% concordance with 126 previously sequenced clinical samples
- Full Hereditary High Cholesterol Genetic Test Validation study available at https://static.getcolor.com/pdfs/whitePaperfh3.pdf
- CAP #8975161, CLIA #05D2081492, CE Marked, NYSDOH approved

Cost-effectiveness

JAMA Oncology: Universal *BRCA1/2* testing is cost-effective at Color's price

Cost-effectiveness of testing strategies in the US



Population and test	ICER	Cost-effective?
Overall population		
Myriad	>$1.7 million per QALY	No
Ambry Genetics	>$900K per QALY	No
Color	$53K per QALY	Yes
Ashkenazi Jewish	Cost-savings regardless of test	Yes/ Dominant

Note: QALY = Quality-Adjusted Life Year
Source: JAMA Oncology

Relevant studies include:

- Long EF, Ganz PA. Cost-effectiveness of Universal *BRCA1/2* Screening: Evidence-Based Decision Making. JAMA Oncol. 2015;1(9):1217-1218. JAMA Article.
- Bennette CS, et al. The cost-effectiveness of returning incidental findings from next-generation genomic sequencing. Genet Med. 2015 Jul;17(7):587-95. PubMed Article.
- Manchanda et al. Cost-effectiveness of Population-Based BRCA1, BRCA2, RAD51C, RAD51D, BRIP1, PALB2 Mutation Testing in Unselected General Population Women. Journal of the National Cancer Institute. 2018.

Genetic testing for Familial Hypercholesterolemia can be cost-effective

A study that conducted DNA testing on families with a known genetic defect to identify new cases of FH before there was an onset of symptoms, found that genetic testing for FH can be cost-effective. Most patients who were newly identified as having FH through the screening program began a cholesterol-lowering statin treatment, and on average, gained 3.3 years of life each.

Taking into account the average total lifetime incremental costs, including costs for screening and testing, lifetime drug treatment, and treatment of cardiovascular events, the cost per QALY was $8,700 US Dollars, falling far below the U.S. benchmark of $50,000 to $100,000 per QALY for population-wide recommended screenings.

Relevant studies include:

- Wonderling D, et al. Cost-effectiveness analysis of the genetic screening program for familial hypercholesterolemia in The Netherlands. Semin Vasc Med. 2004 Feb;4(1):97-104. PubMed Article.

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Clinical Validity

Disease name and MIM number	MedGen	Gene via Genetic Test Registry	Clinical Validity	Actionability and total SQM score
Breast-ovarian cancer, familial 1 (MIM 604370)	MedGen	BRCA1(MIM 113705)	GeneReviews, Molecular Genetics	Details, 10AA
Breast-ovarian cancer, familial 2 (MIM 612555)	MedGen	BRCA2(MIM 600185)	GeneReviews, Molecular Genetics	Details, 10AA
Familial Hypercholesterolemia (MIM 143890)	MedGen	APOB(MIM 107730)	GeneReviews, Molecular Genetics	Details, 11CA
		LDLR(MIM 606945)	GeneReviews, Molecular Genetics	Details, 11CA
Hypercholesterolemia, autosomal dominant, 3 (MIM 603776)	MedGen	PCSK9(MIM 607786)	GeneReviews, Molecular Genetics	Details, 11CA
Lynch syndrome (MIM 120435)	MedGen	MLH1(MIM 120436)	GeneReviews, Molecular Genetics	Details, 10AA, 9AB
	MedGen	MSH2(MIM 609309)	GeneReviews, Molecular Genetics	Details, 10AA, 9AB
	MedGen	MSH6(MIM 600678)	GeneReviews, Molecular Genetics	Details, 10AA, 9AB
	MedGen	PMS2(MIM 600259)	GeneReviews, Molecular Genetics	Details, 10AA, 9AB
		EPCAM(MIM 185535)	GeneReviews, Molecular Genetics	Details, 10AA, 9AB

Online Mendelian Inheritance in Man: OMIM is a comprehensive, authoritative compendium of human genes and genetic phenotypes that is freely available and updated daily. The full-text, referenced overviews in OMIM contain information on all known mendelian disorders and over 15,000 genes. OMIM focuses on the relationship between phenotype and genotype. It is updated daily, and the entries contain copious links to other genetics resources.

MedGen: Organizes information related to human medical genetics, such as attributes of conditions with a genetic contribution.

Genetic Test Registry (GTR): Provides a central location for voluntary submission of genetic test information by providers. The scope includes the test's purpose, methodology, validity, evidence of the test's usefulness, and laboratory contacts and credentials. The overarching goal of the GTR is to advance the public health and research into the genetic basis of health and disease

GeneReviews: An international point-of-care resource for busy clinicians, provides clinically relevant and medically actionable information for inherited conditions in a standardized journal-style format, covering diagnosis, management, and genetic counseling for patients and their families. Each chapter in GeneReviews is written by one or more experts on the specific condition or disease and goes through a rigorous editing and peer review process before being published online.

ClinGen Actionability: The ClinGen Actionability working group has developed a practical, standardized protocol to identify available evidence and generate qualitative summary reports of actionability for disorders and associated genes, as well as a semiquantitative metric to score actionability.

Clinical validity resources

Penetrance determined from population-based studies

Akbar et al. Coming of age in Canada: a study of population-based genetic testing for breast and ovarian cancer. *Current Oncology*. 2017.

Metcalfe et al. The risk of breast cancer in BRCA1 and BRCA2 mutation carriers without a first-degree relative with breast cancer. *Clinical Genetics*. 2018.

Gabai-Kapara et al. Population-based screening for breast and ovarian cancer risk due to BRCA1 and BRCA2. *Proceedings of the National Academy of Sciences of the United States of America*. 2014.

Kuchenbaecker et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. *JAMA*. 2017.

Mavaddat et al. Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE. *Journal of the National Cancer Institute*. 2013.

Pearlman et al. Prevalence and Spectrum of Germline Cancer Susceptibility Gene Mutations Among Patients With Early-Onset Colorectal Cancer. *JAMA*. 2017.

Stoffel et al. Germline Genetic Features of Young Individuals With Colorectal Cancer. *Gastroenterology*. 2018.

Abul-Husn et al. Genetic identification of familial hypercholesterolemia within a single U.S. health care system. *Science*. 2016.

Akioyamen et al. Estimating the prevalence of heterozygous familial hypercholesterolaemia: a systematic review and meta-analysis. *Science*. 2017.

Khera et al. Diagnostic Yield and Clinical Utility of Sequencing Familial Hypercholesterolemia Genes in Patients With Severe Hypercholesterolemia. *Journal of the American College of Cardiology.* 2016.

Current criteria-based approach is missing ~30% to 50% of high-risk people

Grindedal et al. Current guidelines for BRCA testing of breast cancer patients are insufficient to detect all mutation carriers. *BMC Cancer*. 2017.

Møller et al. Genetic epidemiology of BRCA mutations--family history detects less than 50% of the mutation carriers. *European Journal of Cancer.* 2007.

Nilsson et al. Efficacy versus effectiveness of clinical genetic testing criteria for BRCA1 and BRCA2 hereditary mutations in incident breast cancer. *Familial Cancer*. 2017.

Buchanan et al. Early cancer diagnoses through BRCA1/2 screening of unselected adult biobank participants. *Genetics in Medicine.* 2018.

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Chen et al. Low Prevalence of Criteria for Early Screening in Young-Onset Colorectal Cancer. *American Journal of Preventive Medicine.* 2017.

Akioyamen et al. Estimating the prevalence of heterozygous familial hypercholesterolaemia: a systematic review and meta-analysis. *Science*. 2017.

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2. Hampel & de la Chapelle. The Search for Unaffected Individuals with Lynch Syndrome: Do the Ends Justify the Means? *Cancer Prevention Research*. 2011.
3. Nordestgaard et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. *European Heart Journal.* 2013.
4. Plichta et al. What's New in Genetic Testing for Cancer Susceptibility? *Oncology Journal*. 2016.
5. Drohan et al. Hereditary Breast and Ovarian Cancer and Other Hereditary Syndromes: Using Technology to Identify Carriers. *Annals of Surgical Oncology*. 2012.