

## Genomic Tests by Levels of Evidence

Last Updated: 4/15/2013

The [CDC Office of Public Health Genomics](#) provides the following list of genomic tests and family health history in practice according to three levels of evidence based on the paper by [Khoury](#). This list is provided only for informational purposes to researchers, providers, public health programs and others. The list is updated on an ongoing basis. The list below is also available online by searching the [Evidence Aggregator](#) in the [Genomic Applications in Practice and Prevention \(GAPPKb\) database](#).

**Tier 1 genomic and family health history applications are recommended for clinical use by evidence-based panels based on a systematic review of analytic validity, clinical validity and utility for specific clinical scenarios**

| Test/Application  | Scenario  | Evidence-based recommendation  |
|---|---|--|
| Newborn screening panel of 31 core conditions               | Screening all newborns at birth through public health programs  | <a href="#">Secretary's Advisory Committee on Heritable Diseases of Newborns and Children</a> (2011)   |
| <i>BRCA</i> genetic counseling/ <i>BRCA</i> genetic testing | Referral to genetic counseling of women with specific family history patterns of breast or ovarian cancer                                 | <a href="#">US Preventive Services Task Force</a> (2005) [ <a href="#">Update in progress</a> ]<br><br>Additional Information:<br><a href="#">NCCN Guideline: Genetic/Familial High-Risk Assessment: Breast and Ovarian Cancer</a> (2012)  |
| Lynch syndrome testing                                      | Screening newly diagnosed cases of colorectal cancer for Lynch syndrome and cascade testing of relatives of affected Lynch syndrome cases | <a href="#">Recommendations of the EGAPP Working Group: genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives</a> (2009)<br><br>Additional Information:<br><a href="#">NCCN Task Force Report: Evaluating the Clinical Utility of Tumor Markers in Oncology</a> (2011) |
| Familial Hypercholesterolemia                               | Cascade cholesterol testing with/without DNA analysis among relatives of affected persons with familial hypercholesterolemia              | <a href="#">NICE Guideline: Identification and management of familial hypercholesterolaemia</a> (2008)   |
| HLA testing for abacavir sensitivity                        | Testing HIV patients before starting abacavir to reduce adverse effects and inform drug choice  | <a href="#">DHHS Advisory Committee on HIV treatment: Guidelines for the Use of Antiretroviral Agents in HIV-1-infected</a>  |

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|  |  | <a href="#">Adults and Adolescents</a> (2012)  |
| <i>HER2</i> mutation testing in breast cancer  | Routine testing for <i>HER2</i> mutations in patients with invasive breast cancer to target therapy  | <p><a href="#">NICE Guideline: Early and locally advanced breast cancer: diagnosis and treatment</a> (2009)</p> <p>Additional Information:<br/> <a href="#">American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer</a> (2007)</p>  |
| <i>EGFR</i> mutation tumor analysis in Non-small Cell Lung Cancer                                  | Testing for <i>EGFR</i> -positive mutation in patients with non-small cell lung cancer (NSCLC) to target tyrosine kinase inhibitor (TKI) therapy | <p><a href="#">NICE Guideline: Erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small cell lung cancer</a> (2012)</p> <p>Additional information:<br/> <a href="#">NCCN Clinical Practice Guidelines in Oncology: Non–Small Cell Lung Cancer. Version 3</a> (2012) [by free subscription only]</p> <p><a href="#">BCBSA Tec Evaluation - Epidermal Growth Factor Receptor Mutations and Tyrosine Kinase Inhibitor Therapy in Advanced Non-Small-Cell Lung Cancer</a> (2011)</p>   |
| <i>KRAS</i> mutation analysis in patients with mCRC being considered for anti- <i>EGFR</i> therapy | Pharmacogenomic; prediction of non-response to cetuximab and panitumumab   | <p><a href="#">Recommendations from the EGAPP Working Group: Can testing of tumor tissue for mutations in EGFR pathway downstream effector genes in patients with metastatic colorectal cancer improve health outcomes by guiding decisions regarding anti-EGFR therapy?</a> (2013)</p> <p><a href="#">NCCN Task Force Report: Evaluating the Clinical Utility of Tumor Markers in Oncology.</a> (2011)</p> <p><a href="#">American Society of Clinical Oncology provisional clinical opinion: testing for KRAS gene mutations in patients with metastatic colorectal carcinoma to predict response to anti-epidermal growth factor receptor monoclonal antibody therapy.</a> (2009)</p> <p>BCBSA TEC: <i>KRAS</i> Mutations and</p> |

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|  |  | Epidermal Growth Factor Receptor Inhibitor Therapy in Metastatic Colorectal Cancer. (2009, BCBSA personal communication)                                 |
| First-degree family history of breast cancer   | To inform discussion of chemoprevention for breast cancer for women; consider with age and other risk factors to identify high risk for breast cancer and low risk for adverse effects | <a href="#">US Preventive Services Task Force: Chemoprevention of Breast Cancer</a> (2002)   |
| Family history of cardiovascular disease before age 50 years in male relatives and age 60 years in female relatives      | To inform earlier start to screening for cholesterol abnormalities for men and women (starting at age 20 years); use to identify increased risk for lipid disorders                    | <a href="#">US Preventive Services Task Force: Screening for Lipid Disorders in Adults</a> (2008)  |
| Parental history of fracture   | To inform (in combination with other risk factors) earlier start to screening for osteoporosis in women  | <a href="#">US Preventive Services Task Force: Screening for Osteoporosis</a> (2011)   |
| Family history, especially siblings, with hereditary hemochromatosis   | Counseling for genetic testing for hereditary hemochromatosis among asymptomatic people  | <a href="#">US Preventive Services Task Force: Screening for Hemochromatosis</a> (2006)  |
| Family history of breast or ovarian cancer that includes a relative with a <i>known</i> deleterious <i>BRCA</i> mutation | Referral to counseling for BRCA genetic testing for women  | <a href="#">US Preventive Services Task Force: Genetic Risk Assessment and BRCA Mutation Testing for Breast and Ovarian Cancer Susceptibility</a> (2005) |

**Tier 2 genomic and family health history applications have demonstrated analytic and clinical validity; hold promise for clinical utility but evidence-based panels have not examined their use or found insufficient evidence for their use. Such applications may provide information for informed decision making by providers and patients**

| Test/Application  | Scenario  | Evidence-based recommendation  |
|---|---|--|
| Breast cancer gene expression profiles                                  | To estimate risk of recurrence of breast cancer and target therapy  | <p><a href="#">Recommendations from the EGAPP Working Group: Can tumor gene expression profiling improve outcomes in patients with breast cancer? (2009)</a></p> <p><a href="#">NCCN Task Force Report: Evaluating the Clinical Utility of Tumor Markers in Oncology (2011)</a></p>  |
| Oncotype Dx in ER+/node negative patients                               | Prognostic risk recurrence and selection of treatment   | <p><a href="#">NCCN Task Force Report: Evaluating the Clinical Utility of Tumor Markers in Oncology (2011)</a></p>   |
| ER-alpha/PgR (ESR1/PR) tumor protein analysis in Breast Cancer patients | To estimate the prognostic and predictive response to ER-alpha (ESR1)-modulating agents                     | <p><a href="#">NCCN Task Force Report: Evaluating the Clinical Utility of Tumor Markers in Oncology (2011)</a></p> <p><a href="#">NCCN Task Force Report: Estrogen receptor and progesterone receptor testing in breast cancer immunohistochemistry (2009)</a></p> <p><a href="#">American Society of Clinical Oncology/College of American Pathologist guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer (2010)</a></p> |
| <i>KRAS</i> mutations [except c38G>A] NSCLC tumor analysis              | Predictive (negative for anti-EGFR therapy); negatively prognostic in several first-line randomized studies | <p><a href="#">NCCN Task Force Report: Evaluating the Clinical Utility of Tumor Markers in Oncology (2011)</a></p>   |
| CEACAM5 (CEA) serum analysis in colon cancer                            | Baseline monitoring/regular testing for surveillance for Colon Cancer                                       | <p><a href="#">NCCN Task Force Report: Evaluating the Clinical Utility of Tumor Markers in Oncology (2011)</a></p> <p><a href="#">NCCN Clinical Practice Guidelines in</a></p>   |

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|   |  | <p><a href="#">Oncology: Colon Cancer. Version 3</a> (2012)<br/>[by free subscription only]</p> <p><a href="#">ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer</a> (2006)</p>  |
| <p><i>BRAF</i> c.1799T&gt;A (p.V600E) mutation tumor analysis in colon cancer</p>             | <p>Prognostic (negative prognostic marker); Predictive (negative for anti-EGFR therapy) in colon cancer patients</p> | <p><a href="#">NCCN Task Force Report: Evaluating the Clinical Utility of Tumor Markers in Oncology</a> (2011)</p> <p><a href="#">NCCN Clinical Practice Guidelines in Oncology: Colon Cancer. Version 3</a> (2012)<br/>[by free subscription only]</p>  |
| <p><i>BRAF</i> V600E testing in patients with mCRC being considered for anti-EGFR therapy</p> | <p>Pharmacogenomic; prediction of non-response to cetuximab and panitumumab</p>                                      | <p><a href="#">Recommendations from the EGAPP Working Group: Can testing of tumor tissue for mutations in EGFR pathway downstream effector genes in patients with metastatic colorectal cancer improve health outcomes by guiding decisions regarding anti-EGFR therapy?</a> (2013)</p> <p><a href="#">NCCN Task Force Report: Evaluating the Clinical Utility of Tumor Markers in Oncology.</a> (2011)</p> <p><a href="#">Systematic review of pharmacogenetic testing for predicting clinical benefit to anti-EGFR therapy in metastatic colorectal cancer.</a> (2009)</p> |
| <p><i>ALK</i> gene fusion tumor analysis</p>  | <p>Predictive for crizotinib therapy</p>   | <p><a href="#">NCCN Task Force Report: Evaluating the Clinical Utility of Tumor Markers in Oncology</a> (2011)</p> <p><a href="#">NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Version 2</a> (2012) [by free subscription only]</p>  |
| <p>FLT3-ITD tumor analysis for Acute Myeloid Leukemia</p>                                     | <p>Predictive/prognostic FLT3-ITD confers poor risk status</p>   | <p><a href="#">NCCN Task Force Report: Evaluating the Clinical Utility of Tumor Markers in Oncology</a> (2011)</p> <p><a href="#">NCCN Clinical Practice Guidelines in Oncology: Acute Myeloid Leukemia. Version 2</a> (2011) [by free subscription only]</p>  |

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| <i>CEBPA</i> mutation tumor analysis for Acute Myeloid Leukemia   | Predictive/prognostic may confer better risk status   | <a href="#">NCCN Task Force Report: Evaluating the Clinical Utility of Tumor Markers in Oncology</a> (2011)     |
| <i>NPM1</i> mutation tumor analysis for Acute Myeloid Leukemia  | Predictive/prognostic may confer better risk status   | <a href="#">NCCN Task Force Report: Evaluating the Clinical Utility of Tumor Markers in Oncology</a> (2011)     |
| <i>KIT</i> mutation tumor analysis for Acute Myeloid Leukemia   | Predictive/prognostic may confer higher risk of relapse   | <a href="#">NCCN Task Force Report: Evaluating the Clinical Utility of Tumor Markers in Oncology</a> (2011)     |
| First-degree family history of abdominal aortic aneurysm requiring surgical repair                            | Consider for identifying men and women for one-time screening for abdominal aortic aneurysm           | <a href="#">US Preventive Services Task Force: Screening for Abdominal Aortic Aneurysm</a> (2005)               |
| First-degree family history of colorectal cancer at a younger age or multiple affected first-degree relatives | Consider to inform earlier start to colorectal cancer screening for men and women;                    | <a href="#">US Preventive Services Task Force: Screening for Colorectal Cancer</a> (2008)                       |
| Parental history of depression  | Consider with other risk factors when screening adolescents for major depressive disorder             | <a href="#">US Preventive Services Task Force: Major Depressive Disorder in Children and Adolescents</a> (2009) |
| Family history of depression  | Consider with other risk factors when screening adults for depression                                 | <a href="#">US Preventive Services Task Force: Screening for Depression in Adults</a> (2009)                    |
| Family history of bladder cancer  | Consider with other risk factors when determining whether to screen adults for bladder cancer         | <a href="#">US Preventive Services Task Force: Screening for Bladder Cancer in Adults</a> (2011)                |
| Family history of developmental dysplasia of the hip (DDH)  | Consider with other risk factors when determining whether to screen infants for DDH                   | <a href="#">US Preventive Services Task Force: Screening for Developmental Dysplasia of the Hip</a> (2006)      |
| Family history of diabetes  | Consider with other risk factors when determining whether to screen for gestational diabetes mellitus | <a href="#">US Preventive Services Task Force: Screening for Gestational Diabetes Mellitus</a> (2008)           |
| Family history of   | Consider with other risk factors  | <a href="#">US Preventive Services Task Force:</a>  |

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| neonatal jaundice   | when determining whether to screen infants for hyperbilirubinemia  | <a href="#">Screening Infants for Hyperbilirubinemia to Prevent Chronic Bilirubin Encephalopathy (2009)</a>  |
| Family history of age-related macular degeneration            | Consider with other risk factors when determining whether to screen older adults for visual acuity   | <a href="#">US Preventive Services Task Force: Screening for Impaired Visual Acuity in Older Adults (2009)</a>   |
| Family history relevant to dyslipidemia (otherwise undefined) | Consider with other risk factors when determining whether to screen infants, children, adolescents, or young adults (up to age 20 for lipid disorders) | <a href="#">US Preventive Services Task Force: Screening for Lipid Disorders in Children (2007)</a><br><br>Additional Information:<br><a href="#">Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report</a>   |
| Family history of skin cancer                                 | Consider with other risk factors when determining whether to screen adults for skin cancer   | <a href="#">US Preventive Services Task Force: Screening for Skin Cancer (2009)</a>  |
| Family history of chronic kidney disease                      | Consider with other risk factors when determining whether to screen adults for chronic kidney disease  | <a href="#">US Preventive Services Task Force: Screening for Chronic Kidney Disease (2012)</a>   |
| Family history for common diseases                            | Collecting family history in primary care for risk assessment of common diseases   | <a href="#">NIH state-of science panel found insufficient evidence (2009)</a>  |
| Pharmacogenomic testing                                       | Use of pharmacogenomics tests to inform safety and effectiveness of existing medications   | <a href="#">Pharmacogenomics information on labels of more than 80 FDA approved drugs</a> ; The <a href="#">Clinical Pharmacogenetics Implementation Consortium</a> issues guidelines to help clinicians understand how available genetic test results should be used to optimize drug therapy, rather than whether tests should be ordered. |
| Single gene disorders and chromosomal abnormalities           | Molecular, cytogenetic biochemical and other tests available for the diagnosis, management and carrier testing   | <a href="#">More than 2500 genetic</a> conditions affect millions of individuals. Diagnosis and management of these conditions may require use of genetic tests even without formal evidence synthesis and reviews by  |

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|  | for these disorders | evidence panels. <a href="#">The NIH Genetic Testing Registry</a> has updated information on genetic tests in practice. |
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**Tier 3 genomic and family health history applications have not demonstrated adequate analytic validity, clinical validity, or clinical utility. This also includes applications for which evidence-based panels have recommended against their use based on the synthesis of the balance of benefits and harms. Such applications are not ready for routine practice, but may be considered in clinical and population research.**

| Test/Application   | Scenario  | Evidence-based recommendation  |
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| Hereditary hemochromatosis   | Routine genetic screening for hereditary hemochromatosis in the asymptomatic population.  | <a href="#">US Preventive Services Task Force: Screening for Hemochromatosis</a> (2006)  |
| BRCA genetic counseling, BRCA testing  | Routine referral for genetic counseling or routine BRCA testing for women whose family history is not associated with an increased risk of BRCA mutations | <a href="#">US Preventive Services Task Force: Genetic Risk Assessment and BRCA Mutation Testing for Breast and Ovarian Cancer Susceptibility</a> (2005)   |
| Genetic risk factors for common diseases   | Risk assessment and disease prevention  | Multiple panels have recommended against use of genetic risk factors testing. EGAPP made specific recommendations against testing for <a href="#">factor V Leiden</a> and <a href="#">cardiogenomic profiles</a> |
| Emerging genomic tests found in the CDC's <a href="#">GAPP Finder</a> of the <a href="#">GAPP Knowledge Base</a> | More than 400 genomic tests for various intended uses captured through horizon scanning   | Almost all of these applications (except when listed above) have insufficient information on analytic or clinical validity, or clinical utility  |
| Next Generation Sequencing/ Whole Genome Sequence  | Emerging tools to help with diagnosis of rare familial diseases and provide information for assessing risk for common diseases                            | <a href="#">Rapidly evolving landscape</a> ; gaps in knowledge exist for analytic validity, clinical validity and clinical utility   |
| <i>NRAS</i> or <i>PIK3CA</i> mutation analysis and/or testing for loss of PTEN or AKT protein                    | Pharmacogenomic; prediction of non-response to cetuximab and panitumumab  | <a href="#">Recommendations from the EGAPP Working Group: Can testing of tumor tissue for mutations in EGFR pathway downstream effector genes in patients with metastatic</a>                                    |

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| expression                               |  | <p><a href="#">colorectal cancer improve health outcomes by guiding decisions regarding anti-EGFR therapy?</a> (2013)</p> <p><a href="#">Systematic review of pharmacogenetic testing for predicting clinical benefit to anti-EGFR therapy in metastatic colorectal cancer.</a> (2009)</p> |
| Type 2 Diabetes risk prediction panels   | Assess risk for type 2 diabetes in the general population, on the basis of studies in populations of northern European descent | <p><a href="#">Recommendations from the EGAPP Working Group: Does genomic profiling to assess type 2 diabetes risk improve health outcomes?</a> (2013)</p>   |
| <i>TCF7L2</i> genotyping risk prediction | Assess risk for type 2 diabetes in high-risk individuals   | <p><a href="#">Recommendations from the EGAPP Working Group: Does genomic profiling to assess type 2 diabetes risk improve health outcomes?</a> (2013)</p>   |