SENTARA HEALTH PLANS, INC.
CLINICAL CARE SERVICES

Medical Policy: **Medical 34E**

Subject: **Genetic Testing--Pharmacogenetic Testing**

Also see other Genetic Testing Policies:

See Genetic Testing 34 A	Cancer Prevention, Diagnosis, and Treatment
See Genetic Testing 34 B	Pre-Treatment or Post Intervention
See Genetic Testing 34 C	Cardioneurovascular and Developmental Diagnosis
See Genetic Testing 34 D	Preconceptional /Prenatal /Preimplantation Genetic Testing for Preconceptional /Prenatal /Preimplantation
See Genetic Testing 34 F	Medicare Coverage

Effective Date: January 2012

Review Date: October 2013; 12/15; 4/16

Revised Date: November 2013; 01/14; 3/14; 6/14; 11/14; 12/14; 2/15; 3/15; 4/15; 5/15; 6/15; 10/15; 12/15; 2/16; 4/16; 5/16, 6/16, 8/19, 11/19, 6/20, 9/20, 10/20, 10/21

Covered: **See appropriate benefit document for specific coverage determination.**

Exceptions: **Based on current scientific evidence, the following tests are considered not medically necessary because the results of genetic testing have not been scientifically shown to improve clinical outcomes:**

- ADRA2A
- ADRB1
- AGTR1
- ANKK1

- Apolipoprotein E (Apo E) for determining therapeutic response to lipid-lowering medications
- BDKRB1
- CACNA1C
- Comprehensive Personalized Medicine Panel (81225, 81226, 81227, 81240, 81241, 81291, 81350, 81400, 81401, 81479, 81355)
- COMT
- CYP3A4
- CYP1A2
- CYP2B6
- CYP2C19 except for covered indications below.
- CYP2C8
- CYP2C9
- CYP2D6 except for covered indications below
- CYP2D6 except for covered indications below
- CYP3A5 genes, including common variants *2, *3, *4, *5, *6 AmpliChip Cytochrome P450 (CYP450) Genotyping Test; Invader UGT1A1
- CYP3A65
- DRD2
- DPYD, MTHFR, and TYMS Genes for 5-Fluorouracil Pharmacogenetics;
- EYA1 genetic testing (81405)
- HTR2A
- HTR2C
- MTHFR
- OPRM1
- Pathway Genomics Panels
    1. Mental Health DNA Insight
    2. Healthy Woman DNA Insight
    3. Pain Medication DNA Insight
    4. Cardiac DNA Insight
    5. Healthy Weight DNA Insight
- All PGX Profile Panels offered by G6 Genomics for Cardiology, Urology, Pain Management, Psychiatry and Comprehensive
- PharmaRisk panel
- rxSEEK Epilepsy Drug Metabolism Test (81225, 81227, 81401)
- Repeat/Duplicative genetic testing
- SLCO1B1
- SLC6A4
- SULT4A1

- VKORC1
- UGT1A1 Gene
- UGT1A4
- UGT2B15 gene
- Whole Exome Sequencing (WES);
- Exome Sequence Analysis (**81415, 81416, 81417**)
- Whole-genome sequencing in which a member's entire DNA is sequenced,
- Genome Sequence Analysis **(81425, 81426, 81427)**

Pharmacogenetic screening in the general population is not considered medically necessary due to insufficient published scientific evidence of improved clinical outcomes. Examples include but are not limited of the following:

- SureGene Test for Antipsychotic and Antidepressant Response (STA2R)
- EliteLabs panels
- Genecept™ Assay
- GeneSight® Analgesic
- GeneSight® Psychotropic
- GeneSight® ADHD
- GeneSight MTHFR
- Millennium PGT psychotropic testing

- **Any other test not listed below as covered is considered among those that are not medically necessary due to insufficient published scientific evidence of improved clinical outcomes.**

Authorization: Pre-certification by the Plan is required.

Procedure:
Pharmacogenomics is the study of the role of inherited and acquired genetic variation on drug response. It is distinguished from pharmacogenetics, which focuses on individual candidate genes (identified by approaches such as genome-wide association studies (GWAS), genome-wide expression profiling, or methylation studies) to identify markers across the genome that affect drug metabolism, distribution, receptor targets, and biologic effect.
Autosomal recessive: A genetic condition that appears only in individuals who have received two copies of an autosomal gene, one copy from each parent. The gene is on an autosome, a nonsex chromosome. The parents are carriers who have only one copy

of the gene and do not exhibit the trait because the gene is recessive to its normal counterpart gene.
X-linked recessive inheritance - hereditary pattern in which a recessive gene on the X chromosome results in the manifestation of characteristics in male offspring and a carrier state in female offspring.

Clinical Indications:

Genetic Testing is considered medically necessary for the prevention diagnosis and treatment of patients who meet the following:

- There is sufficient Published Scientific Evidence or 3rd party Consensus in the Medical Community that the results of the specific genetic Testing improves clinical outcomes;

OR

- There is an approved mutation specific treatment available;

AND

- After completion of a thorough history, physical examination, pedigree analysis, genetic counseling, relevant diagnostic and biochemical tests (if any), the patient meets criteria for any of the following approved tests;

AND

- Identification of the gene biomarker is noted to be clinically necessary prior to initiating therapy with the drug target as noted in the section heading "Indications and Usage" of the U.S. Food and Drug Administration (FDA)-approved prescribing label. (**criteria are listed individually for each test below)**

A. HLA-B 1502 with carbamazepine (Tegretol);

OR

B. HLA-B 5701 Screening for Abacavir Hypersensitivity;

OR

C. HIV Drug Susceptibility and Resistance Tests (Phenotypic or Genotypic);

OR

D. CYP2C19 variant of Cytochrome P450 to determine the drug-metabolizer status for clopidogrel;

OR

E. Cystic fibrosis transmembrane conductance regulator (CFTR) potentiator for Kalydeco (ivacaftor).

OR

F. Rasburicase and G6PD testing

OR

G. CYP2D6 polymorphisms (see exclusions above) (**81226**)

OR

H. Methylguanine-DNA methyltransferase(PredictMDxTM) (**81287**)

OR

I. Co-receptor tropism testing (i.e., Trofile™)

OR

J. Congenital sucrose-isomaltase deficiency Testing (CSID)

OR

K. Retinoid isomerohydrolase (RPE65) Gene Testing (Luxturna)

OR

L. HLA-B 58:01 Allopurinol Hypersensitivity Testing

OR

M. Genetic testing to detect somatic/tumor BRCA mutations and or large genomic rearrangements (e.g. myChoice CDx)

OR

N. PD-L1

OR

O. NTRK NGS Fusion Profile

Clinical Indications listed with each test:

A. **HLA-B** (**major histocompatibility complex, class I, B**) is a human gene that provides instructions for making a protein that plays a critical role in the immune system. HLA-B is part of a family of genes called the human leukocyte antigen (HLA) complex. The HLA complex helps the immune system distinguish the body's own proteins from proteins made by foreign invaders such as viruses and bacteria. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) can involve restricted presentation of a drug or its metabolites for T-cell activation. HLA-B(*) 1502 tightly associated with carbamazepine (CBZ) induced these conditions in a Han Chinese population.

Clinical Indications: HLA-B 1502

1. Genotyping for HLA-B* 1502 is medically necessary for persons of **Asian** ancestry before initiating treatment with carbamazepine (Tegretol).

B. **HLA-B*5701 Screening for Abacavir Hypersensitivity**
HLA-B*5701 is a small variation in the genetic structure of a human being. Some people have the variation some do not. Studies now indicate that those people who have the HLA-B*5701 are susceptible to the hypersensitivity reaction to the HIV medication Ziagen (abacavir). HIV specialists are now starting to use the HLA-B*5701 test to help identify

those people who may have a hypersensitivity reaction to Ziagen (abacavir).

Clinical Indications: HLA-B 5701

1. This test is approved for **ANY** HIV member who is being considered for treatment with the HIV medication Ziagen (abacavir) to help avoid an Abacavir Hypersensitivity Reaction.

C. **HIV Drug Susceptibility and Resistance Tests**
(Phenotypic or Genotypic)

Clinical Indications for HIV Drug Susceptibility and Resistance Tests
1. Approved with no criteria.

D**.** **CYP2C19 variant of Cytochrome P450**
Repeat CYP2C19 genotyping has no proven value

Clinical Indications: When used to determine the drug-metabolizer status for clopidogrel:

1. Member is currently undergoing treatment with clopidogrel and has not been tested;

OR

2. Members whom the use of clopidogrel is being proposed.

E**.** **Cystic fibrosis transmembrane conductance regulator (CFTR) potentiator for Kalydeco (ivacaftor)** Kalydeco is classified as a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator. It is indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have a G551D mutation in the CFTR gene.

Clinical Indications: Cystic fibrosis transmembrane conductance regulator (CFTR) potentiator/ Kalydeco (ivacaftor)

1. Member is 6 years of age or older with a diagnosis of Cystic Fibrosis

F. **ELITEK (rasburicase) is an important component of uric acid management associated with tumor lysis syndrome (TLS)**

Clinical Indications for Rasburicase and G6PD testing:
G6PD gene testing may be indicated when **one** of the following is present; Prior to starting therapy with rasburicase and **1 or more** of the following:

1. Female at high risk for G6PD deficiency, including **1 or more** of the following:

   a. History of previous hemolytic episode;

   b. Originating from geographic area with high prevalence of G6PD deficiency

2. Male at high risk for G6PD deficiency and inconclusive results of biochemical testing of enzyme activity;

3. Neonate with history of jaundice.

G**.** **CYP2D6 polymorphisms** CYP2D6 (Cytochrome P450 2D6) acts on 25% of all prescription drugs. Some 7-14% of the population has a slow acting form of this enzyme and 7% a super-fast acting form. Thirty-five percent are carriers of a non-functional CYP2D6 allele, which especially elevates the risk of adverse drug reactions when these individuals are taking multiple drugs.

Clinical Indications for CYP2D6 polymorphisms:

1. For members with Huntington's Disease who have been or who are being considered to be prescribed doses of tetrabenazine (Xenazine) greater than 50 mg per day.

OR

2. For members with Gaucher's disease type 1 who are being considered for treatment with eliglustat (Cerdelga).

OR

3. Amitriptyline or nortriptyline for treatment of depressive disorders

OR

4. Tetrabenazine doses greater than 50 mg/day, or re-initiation of therapy with doses greater than 50 mg/day

H. **PredictMDx for Glioblastoma**, MDxHealth's most advanced product, is a test to identify patients with different prognosis when treated with current standard of care (temozolomide plus radiotherapy) for newly diagnosed glioblastoma patients. The test assesses the methylation status of the MGMT gene, which is a crucial DNA repair gene

Clinical Indications for MGMT (O(6)-methylguanine-DNA methyltransferase) gene methylation assay:

1. For predicting response to temozolomide (Temodar) in persons with glioblastoma.

I. **Co-receptor tropism testing** (i.e., Trofile™) The Trofile (TM) assay is a blood test that identifies the tropism of a patient's HIV. The assay's purpose is to identify the tropism of an individual patient's HIV strain – R5, X4, or a combination of these known as dual/mixed (D/M).

Clinical Indications for Trofile for EITHER of the following:

1. To determine virus tropism prior to initiating a CCR5 antagonist (e.g., Miraviroc [Selzentry])

OR

2. For a member demonstrating virologic failure while receiving therapy that contains a CCR5 antagonist.

J. **Sucrose-isomaltase deficiency Testing**

Clinical Indications for requests meeting ALL of the following criteria:

1. Stool PH <6

AND

2. Increase in breath hydrogen of >10ppm when challenged with Sucrose after fasting

AND

3. Negative Lactose breath test

AND

4. Low sucrose activity on duodenal biopsy

AND

5. Normal other disaccharidases on duodenal biopsy

K. **Retinoid isomerohydrolase (RPE65) Gene Testing**

Retinoid isomerohydrolase (RPE65) Gene Testing ro **ALL** of the following:

1. Testing results will effect treatment the individual is getting

2. Individual's diagnosis is still unclear after documentation all of the following:

    a) Physical examination

    b) Individual's history reviewed

    c) Pedigree analysis

    d) Genetic counselin

    e) Standard diagnostic studies have been completed

3. Individual has indications of 1 or more of the following:

    a) Individual exhibits clinical features

    b) Individual is pre-symptomatic (specific risk of inheriting the mutation)

4. Individual has sufficiently viable retinal cells as determined by optical coherence tomography (OCT) and/or ophthalmoscopy with all of the following:

    a) Individual has 1 or more of the following:

        1) Area of retina within the posterior pole of greater than 100μm thickness per optical coherence tomography (OCT)

        2) At least 3 disc areas of retina without atrophy or pigmentary degeneration within the posterior pole

    b) Individual has 1 or more of the following:

        1) Visual field within 20 degrees in any meridian as measured by III4e isopter OR equivalent in both eyes

        2) Visual acuity worse than 20/60 in both eyes

L. **HLA-B 58:01 Allopurinol Hypersensitivity Testing**

Clinical Indications for requests meeting ALL of the following criteria:

1. This test is approved for individual who is being considered for treatment with the medication Allopurinol and is of Asian descent

M. **Genetic testing to detect somatic/tumor BRCA mutations and or large genomic rearrangements (e.g. myChoice CDx)**

Clinical Indications for requests meeting 1 of the following criteria:

1. Advanced epithelial Ovarian, fallopian tube or primary peritoneal cancer who have been treated with three or more prior lines of chemotherapy and being considered for niraparib (Zejula).

OR

2. Advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in a complete or partial response to two or more lines of platinum-based chemotherapy and are being considered for maintenance treatment with niraparib.

N. PD-L1 testing for triple negative breast cancer (Estrogen, progesterone and HER 2 negative)

O. NTRK NGS Fusion Profile for individual who is an adult or pediatric who has a solid tumor who is being considered for Vitrakvi (larotrectinib) therapy.

CPT/HCPCS:

0172U	Oncology (solid tumor as indicated by the label), somatic mutation analysis of BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) and analysis of homologous recombination deficiency pathways, DNA, formalin-fixed paraffin-embedded tissue, algorithm quantifying tumor genomic instability score
81225	CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *8, *17)
81226	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN)
81287	Methylguanine-DNA methyltransferase
81434	Hereditary retinal disorders (eg, retinitis pigmentosa, Leber congenital amaurosis, cone-rod dystrophy), genomic sequence analysis panel, must include sequencing of at least 15 genes, including ABCA4, CNGA1, CRB1, EYS, PDE6A,

	PDE6B, PRPF31, PRPH2, RDH12, RHO, RP1, RP2, RPE65, RPGR, and USH2A
81381	HLA Class I typing, high resolution (ie, alleles or allele groups); 1 allele or allele group (eg, B*57:01P), each
81479	Unlisted molecular pathology procedure
81599	Unlisted multianalyte assay with algorithmic analysis
88360	Morphometric analysis, tumor immunohistochemistry (eg, Her-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, per specimen, each single antibody stain procedure; manual

---

REFERENCES

___	Agency for Healthcare Research and Quality (AHRQ)		
___	Diagnostic and Therapeutic Technology Assessment (DATTA) Review		
_X_	Specialty Association Guidelines	___	SHC Guidelines
_X_	Government Regulations	_X_	Literature Review
___	Specialty Advisors	_X_	Winifred S. Hayes, Inc.
_X_	UpToDate	_X_	NCD
_X_	LCD	_X_	Relevant Other Payer Approaches

References used include but are not limited to the following:

(2020). Retrieved May 11, 2020, from Centers for Medicare and Medicaid Services: https://www.cms.gov/medicare-coverage-database/search/search-results.aspx?SearchType=Advanced&CoverageSelection=Both&NCSelection=NCA%7cCAL%7cNCD%7cMEDCAC%7cTA%7cMCD&ArticleType=BC%7cSAD%7cRTC%7cReg&PolicyType=Both&s=53&KeyWord=pharmacogenetic&KeyWordLookU

(2020). Retrieved May 12, 2020, from National Comprehensive Cancer Network: https://cse.google.com/cse?cx=007894372670309631110:vocdaeamxuy&ie=UTF-8&q=allopurinol&safe=high

(2020, Feb 05). Retrieved May 12, 2020, from MCG: https://careweb.careguidelines.com/ed23/index.html
(2020). Retrieved May 12, 2020, from Department of Medical Assistance Services: https://www.virginiamedicaid.dmas.virginia.gov/wps/portal/ProviderManual

Allopurinol: Drug information (Lexicomp). (2020). Retrieved May 11, 2020, from UpToDate: https://www.uptodate.com/contents/allopurinol-drug-information?search=hla%20b5801&source=search_result&selectedTitle=3~150&usage_type=default&display_rank=3#F131725

Genetic Testing to Predict Allopurinol Toxicity. (2019, Aug 29). Retrieved May 11, 2020, from Hayes, Inc.: https://evidence.hayesinc.com/report/gti.predictallopurinol3969

Gout. (2020). Retrieved May 11, 2020, from American College of Rheumatology: https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines/Gout

Hyperuricemia and Gout in Chronic Kidney Disease. (2019, Jul 25). Retrieved May 12, 2020, from DynaMed: https://www.dynamed.com/condition/hyperuricemia-and-gout-in-chronic-kidney-disease

Pharmacogenomic Testing and Genetic Testing for Thrombotic Disorders. (2020, Mar 03). Retrieved May 12, 2020, from AIM Specialty Health: https://aimproviders.com/genetictesting/wp-content/uploads/sites/15/2019/12/PharmacogeneticandThrombophilia_Mar_2020.pdf

Redwood, A. J., Pavlos, R. K., White, K. D., & Phillips, E. J. (2018, Jan). HLAs: Key Regulators of T-cell-mediated Drug Hypersensitivity. Retrieved May 12, 2020, from PubMed: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5743596/

(2019, Sep 10). Retrieved Sep 18, 2019, from Genetics Home Reference: https://ghr.nlm.nih.gov/gene/RPE65#synonyms

(2019). Retrieved Sep 19, 2019, from Hayes, Inc.: https://evidence.hayesinc.com/search?q=%257B%2522phrase%2522:%2522Invitae%2520Singel%2520gene%2522,%2522style%2522:%2522PHRASE%2522,%2522size%2522:10,%2522page%2522:1,%2522bundle%2522:%257B%2522path%2522:%2522%2522,%2522title%2522:%2522%2522%257D,%2522tot

(2019). Retrieved Sep 19, 2019, from AIM Specialty Health: https://aimspecialtyhealth.com/resources/clinical-guidelines/genetic-testing/

(2019). Retrieved Sep 19, 2019, from National Comprehensive Cancer Network: https://cse.google.com/cse?cx=007894372670309631110:vocdaeamxuy&ie=UTF-8&q=RPE65&safe=high

About Luxturna. (2019). Retrieved Sep 18, 2018, from Spark Therapeutics: https://luxturna.com/about-luxturna/
LCD: Voretigene Neparvovec-rzyl (Luxturna) (L37863). (2019, Sep 05). Retrieved Sep 19, 2019, from Centers for Medicare and Medicaid Services: https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=37863&ver=11&SearchType=Advanced&CoverageSelection=Both&NCSelection=NCA%7cCAL%7cNCD%7cMEDCAC%7cTA%7cMCD&ArticleType=BC%7cSAD%7cRTC%7cReg&PolicyType=Both&s=53&KeyWord=RPE65&KeyWo

Recommendations on Clinical Assessment of Patients with Inherited Retinal Degenerations - 2016. (2016, Jun). Retrieved Sep 19, 2019, from American Academy of Ophthalmology: https://www.aao.org/clinical-statement/recommendations-on-clinical-assessment-of-patients

Retinal Disorders - Gene Panels, A-0912. (2019, Feb 11). Retrieved Sep 19, 2019, from MCG: https://careweb.careguidelines.com/ed23/index.html

Retinitis pigmentosa: Treatment. (2018, Apr 11). Retrieved Sep 19, 2019, from UpToDate: https://www.uptodate.com/contents/retinitis-pigmentosa-treatment?search=RPE65&source=search_result&selectedTitle=1~4&usage_type=default&display_rank=1

Retinitis Pigmentosa. (2019, Nov 18). Retrieved Sep 19, 2019, from DynaMed: https://www.dynamed.com/condition/retinitis-pigmentosa#GUID-E50FA4AE-CEB8-4AB3-B3D8-F1F06CB66D7C

RPE65. (2019). Retrieved Sep 18, 2019, from Invitae: https://www.invitae.com/en/physician/genes/21284/
16. RPE65 single gene test. (2019). Retrieved Sep 19, 2019, from Blueprint Genetics: https://blueprintgenetics.com/tests/single-gene-tests/rpe65-single-gene-test-2/

Pao W, Miller V, Zakowski M, et al. EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. Proc Natl Acad Sci U S A 2004; 101:13306.

Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 2004; 350:2129.

Paez JG, Jänne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 2004; 304:1497.

Keedy VL, Temin S, Somerfield MR, et al. American Society of Clinical Oncology provisional clinical opinion: epidermal growth factor receptor (EGFR) Mutation testing for patients with advanced non-small-cell lung cancer considering first-line EGFR tyrosine kinase inhibitor therapy. J Clin Oncol 2011; 29:2121.

Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009; 361:947.

Fukuoka M, Wu YL, Thongprasert S, et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). J Clin Oncol 2011; 29:2866.

Leufkens HG. The interface between pharmacoepidemiology and pharmacogenetics. Eur J Pharmacol 2000; 410:121.

Ingelman-Sundberg M. Pharmacogenetics: an opportunity for a safer and more efficient pharmacotherapy. J Intern Med 2001; 250:186.

Drazen JM, Silverman EK, Lee TH. Heterogeneity of therapeutic responses in asthma. Br Med Bull 2000; 56:1054.

Evans WE, McLeod HL. Pharmacogenomics--drug disposition, drug targets, and side effects. N Engl J Med 2003; 348:538.

Wang L, McLeod HL, Weinshilboum RM. Genomics and drug response. N Engl J Med 2011; 364:1144.

Vesell ES. Therapeutic lessons from pharmacogenetics. Ann Intern Med 1997; 126:653.

Evans WE, Relling MV. Pharmacogenomics: translating functional genomics into rational therapeutics. Science 1999; 286:487.

Mancinelli L, Cronin M, Sadée W. Pharmacogenomics: the promise of personalized medicine. AAPS PharmSci 2000; 2:E4.

Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA 1998; 279:1200.

Kongkaew C, Noyce PR, Ashcroft DM. Hospital admissions associated with adverse drug reactions: a systematic review of prospective observational studies. Ann Pharmacother 2008; 42:1017.