Health Evidence Review Commission's Genetics Advisory Panel

October 23, 2019

9:00 AM - 11:00 PM

Teleconference
Suite 775, Transformation Center Conference Room
421 SW Oak Street, Portland, Oregon

Section 1.0

Call to Order

AGENDA
HERC's Genetics Advisory Panel (GAP)
October 23, 2019
9:00 am – 11:00 am
Teleconference
Public location: Five Oak Building
Transformation Center Conference Room
421 SW Oak Street, Suite 775
Portland, OR 97204

(All agenda items are subject to change and times listed are approximate)

#	Time	Item	Presenter
1	9:00 AM	Call to Order & Introductions	Karen Kovak
2	9:05 AM	Staff report	Ariel Smits
3	9:15 AM	2020 CPT codes related to cancer oncology	Ariel Smits
4	9:45 AM	Non-prenatal, non-cancer genetic testing guideline a) Cytochrome P450 genetic testing b) Microarray analysis c) Whole exome sequencing coverage	Ariel Smits
5	10:15 AM	Prenatal genetic testing guideline a) CF genetic testing code	Ariel Smits
6	10:30 AM	Hereditary cancer genetic testing guideline a) NCCN reference updates b) CALR genetic testing for myeloproliferative disease c) Hereditary breast cancer-related disorders genomic sequence analysis panels	Ariel Smits
7	10:50 AM	Other business	Ariel Smits
8	10:55 AM	Public comment on topics not on agenda above	
7	11:00 AM	Adjournment	Karen Kovak

Note: Public testimony will be taken on each topic per HERC policy at the time at which that topic is discussed. Public testimony not related to a topic on the agenda will be taken at the end of the meeting.

Highlights

Genetic Advisory Panel
Conference Call hosted at:
Lincolin Building
421 SW Oak Street, Suite 750
OEI Conference Room
Portland, OR 97204
October 10, 2018
9:00-12:00 a.m.

Members Present: Karen Kovak; Catherine Murray; Nicoletta Voian

Staff Present: Ariel Smits, MD, MPH; Jason Gingerich

Also Attending: Jim Gajewski (OASCO), Jim Clark and Ashley Allen from Roche Diagnostics; Devki Saraya and Karen Heller from Myriad; Ashley Svensen from Counsyl; Andrew Yu from NW Oncology

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The meeting was called to order at 9AM. Roll was called. The highlights from the 2017 GAP meeting were reviewed and no changes were suggested.

Review of New Genetics CPT Codes for 2019

The 2019 Genetic CPT codes were reviewed. There were no suggested changed from the staff recommendations. Specific code discussions:

1) CPT **81329** (SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; dosage/deletion analysis (eg, carrier testing), includes SMN2 (survival of motor neuron 2, centromeric) analysis, if performed) is a prental genetic test for carrier status. It should be included on the prenatal genetic testing guideline. It is replaceing CPT 81401 as the code for this test, which is a non-specific code. Smits will make this change to the prenatal testing guideline.
2) CPT **81443** (Genetic testing for severe inherited conditions (eg, cystic fibrosis, Ashkenazi Jewish-associated disorders [eg, Bloom syndrome, Canavan disease, Fanconi anemia type C, mucolipidosis type VI, Gaucher disease, Tay-Sachs disease], beta hemoglobinopathies, phenylketonuria, galactosemia), genomic sequence analysis panel, must include sequencing of at least 15 genes).
    a. Gap discussion: This test is a big panel offered for carrier testing for prenatal or preconception counseling/testing. Panel tests used now have 170+ genes. Could be used for any panel 15 genes or larger. The reason this CPT code was added was that the

same code is to be used for any panel with one rate of reimbursement. All GAP members felt that this was reasonable to cover. Often cost is the same to test for a single gene as a panel. All pregnant patients should be offered expanded carrier screening per ACOG guidleines. It was noted that carrier panel testing is specifically excluded currently in the prenatal testing guideline, but the rationale for that exclusion was not recalled. Gingerich felt that it was likely a result of the coverage guidance done on this topic some years ago.

a. Public testimony: Ashley Spensen with Counsyl: this code is for over 15 genes. ACOG committee opinion is that over 15 genes in one panel is an acceptable strategy. Over ½ of all screening in US is now done with expanded panel tests. ACOG has criteria, requires that a panel must have childhood onset, have a 1 in 100 carrier frequency, etc. This can be found in ACOG committee opinions 690 and 691. The purpose of this new code is to prevent code stacking. Consider coverage for a limited group of patients (adopted, unexplained family history, h/o repeated miscarriages).
b. Decision: HERC staff will identify the ACOG guidelines referenced (#690 and #691). Staff will also research why carrier panel testing was specifically excluded from the prenatal genetic testing guideline. The GAP recommendation is to place this code on the Diagnostic Procedures File, and staff will have this further research done prior to the VBBS discussion of this recommendation. Staff will work on edits to the prenatal genetic testing guideline regarding this test and circulate among GAP members for final approval.

Review of the Non-prenatal Genetic Testing Guideline

Smits first reviewed the annual updates required for the NCCN guidelines and changes required for the 2019 CPT codes. There was no discussion of this section. Smits then reviewed the requests for changes to the guideline from Myriad. The GAP members agreed that the hereditary cancer testing section should be revmoed from the larger guideline and become its own guideline. Hereditary cancer testing is different than other genetic testing in symptomatic individuals, and has extensive guidelines from NCCN governing utilization. This will help clarify that hereditary cancer testing does not fall under the 10% probability of finding a genetic mutation required in the larger non-prenatal genetic testing guideline.

Withing hereditary cancer genetic testing, the GAP agreed that the section on breast and ovarian cancer syndrome genetic testing for patients with a history of cnacer should have “women” changed to “patient” to include men with a history of breast or associated cancers. The section for patients without a personal history of cancer should be changed to include other associated cancers which are included in NCCN guidelines.

There was discussion about the suggested wording changes to the hereditary cancer panel testing section. The GAP members felt that this section should not be restricted to just colon and breast/ovarian cancer, as there are many other hereditary cancer syndromes. They approved removing the section requiring the panel to have at least 5 genes mentioned in the NCCN breast/ovarian or colon cancer guidelines and remove

the limit of "a reasonable number of genes." GAP member noted that they routinely use panel testing rather than single or a few gene tests, and that these panels are more cost effective. Many of these panels have 150+ genes.

There was extensive discussion regarding who should be allowed to provide genetic counseling in the guideline. Currently, only providers with board certification or eligibility in certain genetic related areas are acceptable as genetic counselors. Myriad requested broadening this out to include a wide variety of providers, including PCPs. GAP members noted that this was consistent with NCCN guidelines, but expressed concern that some providers might be well trained and experienced, while others may not be. There was concern that without a demonstrable board certification, there would be no way to verify training and experience. If the counseling requirement is changed, the GAP members felt that the term "genetic counseling" needed to be changed to "informed consent" as most of these provider types did not actually do genetic counseling. Generally, GAP members were uncomfortable with broadening the range of providers for genetic counseling. Access was noted to be limited in certain areas of the state to genetic counselors, although there has been more work on virtual visits. The GAP members did note that hereditary cancer testing should be opened to any provider mentioned in the NCCN guidelines. For the new hereditary cancer guideline, they suggested taking out the wording specifying the type of provider. However, this wording should be left in the general non-prenatal genetic testing guideline. If this suggestion is not acceptable to the HERC, the GAP suggests convening a work group on genetic counseling, with hereditary cancer testing separated from cancer testing and other types of genetic testing. This workgroup should balance access with appropriateness of services.

Review of microarray testing

Smits reviewed the summary document and the Washington HTA review of the technology. Kovak was in favor of continuing coverage for microarray testing. In her experience, most of the kids seen for consideration of such testing have more than one symptom. It is rare to see kid for genetic testing with just autism. Kovak felt the testing was appropriate to continue to cover as listed. This testing may also affect reproductive decision making. Most of these conditions are rare individually, so it is hard to find literature on change in outcome for any one condition which might be found on microarray testing. Other GAP members agreed on no change in coverage. GAP members felt that such testing helps to get kids needed services.

Review of the Prenatal Genetic Testing Guideline

Smits reviewed the summary document of suggested changes. There was no discussion of the changes based on 2019 CPT codes in the guideline. Next the group discussed which of the additional CPT codes identified by staff were appropriate to add. This section was reviewed in response to a GAP request that staff identify missing CPT codes for amniocentesis, serum genetic screening, etc. The GAP members agreed to all the staff suggested additions except for 84163, 84702 and 86336, which were not added.

There was discussion about adding male partners of pregnant women to this guideline for women who are found to be the carrier of a recessive condition. The GAP members were unsure if such testing should be added to the prenatal or the non-prenatal genetic testing guideline. Currently, in the non-prenatal guideline, there is wording about testing for carrier status for cystic fibrosis and for Ashkenazi Jewish carrier testing panel. However, spinal muscular atrophy carrier screening is a new 2019 CPT code and not included in the non-prenatal genetic testing guideline. Staff added SMA carrier screening to the non-prenatal genetic testing guideline with the restriction that it be covered once in a lifetime.

The GAP then looked at the remainder of the prenatal genetic screening guideline. Based on the GAP desire to cover 2019 CPT 81443 regarding expanded carrier screening, the GAP recommended deleting section "P. Expanded carrier screening only for those genetic conditions identified above" of the prenatal guideline and section "C. Expanded carrier screening which includes results for conditions not explicitly recommended for coverage" of the section specifying non-covered tests. Staff could not recall why such expanded carrier screening was expressly called out for non coverage. Gingerich thought that it might be due to an old coverage guidance. Staff will research why expanded carrier testing was explicitly excluded in the past and bring this as a separate topic for discussion at the November VBBS/HERC meetings.

GAP members requested that the second genetic screening test explicitly listed for non-coverage, "B. Screening for thrombophilia in the general population or for recurrent pregnancy loss" be reviewed for deletion at the 2019 GAP meeting.

Cell free fetal DNA screening for low risk women

Smits reviewed the summary document and reviewed the literature about the sensitivity, specificity, and economic analyses around non-invasive prenatal screening (NIPS). The GAP discussed that ACOG is expected to be coming out soon with a new guideline recommending universal NIPS screening (high and low risk women). There is concern about use of NIPS to determine the gender of the baby. The GAP members did feel that it was a better screening test for trisomies that traditional screening tests. There is a newer form of NIPS that can also give a pre-eclampsia risk which could allow for treatment with aspirin in pregnancy to lower the risk of pre-eclampsia. GAP members noted that NIPS is a rapidly changing field.

Ashley Allen from Roche Diagnostics noted that NIPS is a more sensitive and specific test that traditional screening, and will reduce the number of women requiring invasive procedures such as amniocensis, which lowers cost and adverse outcomes. She states that most private payers in Oregon (Premara, Regence, Anthem) cover all risk women for NIPS. Not covering for OHP causes disparities.

It was noted by an audience member that the ACOG guideline says that any type of screening is appropriate, but does not say that NIPS should be restricted to high risk women. Therefore, the current ACOG opinion could be interpreted to indicate that ACOG feels that NIPS is appropriate for all risk women. Far more women have false positive tests with traditional screening methods, causing increase invasive testing and expense.

The GAP decision was to make no change in the current restriction of NIPS to high risk women. HERC staff will monitor for the new ACOG statement expected to come out in favor of universal NIPS screening. If ACOG publishes such an opinion, GAP would be in favor of changing the prenatal genetic testing guideline to allow use for low and high risk women. Such a change can be made prior to the next GAP meeting or can be taken up at the 2019 GAP meeting.

Public testimony:
Jim Gejewsky testified that GAP should consider recommending coverage of whole exome sequencing. This test is appropriate for a child with clinical descriptive genetic abnormality and no specific diagnosis. Children and families need a specific diagnosis in many cases to receive services from schools, appropriate medical supportive services, etc.

The GAP members felt that this was worth consideration, but that there were no materials to review for this meeting. Whole exome sequencing will be placed on the agenda for the 2019 GAP meeting. HERC staff were directed to relook at the literature on this topic, including any available MED reports and national guidelines prior to that meeting.

Adjournment
The meeting adjourned at 11:30 AM

Section 3.0

New Codes

2020 CPT Code Review
Oncology

1) PALB2
    a. **CPT 81307** PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) gene analysis; full gene sequence
    b. **CPT 81308** PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) gene analysis; known familial variant
    c. Definition:
        i. This gene encodes a protein that may function in tumor suppression. This protein binds to and colocalizes with the breast cancer 2 early onset protein (BRCA2) in nuclear foci and likely permits the stable intranuclear localization and accumulation of BRCA2
    d. NCCN guidelines
        i. NCCN V3.2019 Breast Cancer: not mentioned
        ii. NCCN V3.2019 High Risk for Breast/Ovarian Cancer
            1. PALB2 positive status changes age of onset for screening for breast cancer and modality of screening—screening beginning at age 30 with consideration for breast MRI as screening modality
            2. Notes that the lifetime breast cancer risk for PALB2+ women is 35%
        iii. NCCN V3.2019 Pancreatic Adenocarcinoma
            1. PALB2 result changes treatment recommendations
        iv. NCCN V1.2019 Myelodysplastic Syndromes
            1. PALB2 mutations noted to be associated with Fanconi anemia
    e. Similar code placement: BRCA testing is Diagnostic
    f. HERC staff recommendation
        i. Add CPT **81307** ad **81308** to the Diagnostic Procedures File

2) PIK3CA
    a. **CPT 81309** PIK3CA (phosphatidylinositol-4, 5-biphosphate 3-kinase, catalytic subunit alpha) (eg, colorectal and breast cancer) gene analysis, targeted sequence analysis (eg, exons 7, 9, 20)
    b. Definition:
        i. Gene amplifications, deletions and more recently, somatic missense mutations in the *PIK3CA* gene have been reported in many human cancer types including cancers of the colon, breast, brain, liver, stomach and lung.
    c. NCCN guidelines
        i. NCCN V3.2019 Breast Cancer
            1. Testing for PIK3CA recommended if considering alpelisib therapy for HR+/HER2- breast cancer
        ii. NCCN V2.2019 Colon Cancer
            1. PIK3CA mutations may predict responsiveness to aspirin, but the data is inconsistent
    d. HERC staff recommendation

i. Add CPT **81309** to line 191 CANCER OF BREAST; AT HIGH RISK OF BREAST CANCER

3) Biomarker tests for cancer tissue
    a. Genome wide microarray testing for cancer
        i. CPT **81277** Cytogenomic neoplasia (genome-wide) microarray analysis, interrogation of genomic regions for copy number and loss-of-heterozygosity variants for chromosomal abnormalities
    b. Review history:
        i. Multiple gene assays for cancer were reviewed in August 2015 by HTAS as part of a biomarkers for cancer review. At that time, one microarray gene expression profiling test (CPT 81504 Oncology (Tissue of origin), microarray gene expression profiling of >2000 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as tissue similarity scores) was specifically reviewed. HTAS recommendation was for non-coverage of all multiple gene assays for cancer (weak recommendation).
    c. Similar codes:
        i. This test was previously reported under CPT 81406 (Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia) ACADVL (acyl-CoA dehydrogenase, very long chain) (eg, very long chain acyl-coenzyme A dehydrogenase deficiency), full gene sequence ACTN4 (actinin, alpha 4) (eg, focal segmental glomerulosclerosis), full gene sequence AFG3L2 (AFG3 ATPase family gene 3-like 2 [S. cerevisiae]) (eg, spinocerebellar ataxia), full gene sequence AIRE (autoimmune regulator) (eg, autoimmune polyendocrinopathy syndrome type 1), full gene sequence ALDH7A1 (aldehyde dehydrogenase 7 family, member A1) (eg, pyridoxine-dependent epilepsy), full gene sequence ANO5 (anoctamin 5) (eg, limb-girdle muscular dystrophy), full gene sequence ANOS1 (anosmin-1) (eg, Kallmann syndrome 1), full gene sequence APP (amyloid beta [A4] precursor protein) (eg, Alzheimer disease), full gene sequence ASS1 (argininosuccinate synthase 1))
            1. Diagnostic Procedures File
        ii. Evidence
            1. No literature found
        iii. Expert input:
            1. Providence Oncology group agreed with the staff recommendation
        iv. <u>HERC staff recommendation</u>
            1. Add CPT **81277** (Cytogenomic neoplasia (genome-wide) microarray analysis, interrogation of genomic regions for copy number and loss-of-heterozygosity variants for chromosomal abnormalities) to line 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
            2. Add an entry to GN173 as shown below

d. Endopredict for breast cancer
    i. CPT **81522** Oncology (breast), mRNA, gene expression profiling by RT-PCR of 12 genes (8 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence risk score
    ii. Breast cancer algorithmic tests were reviewed in an HTAS coverage guidance in March, 2018. CPT 81522 appears to represent a test called Endopredict. The coverage guidance recommended that the Endopredict test be covered in certain clinical situations.
    iii. <u>HERC staff recommendation</u>
        1. Add CPT **81522** (Oncology (breast), mRNA, gene expression profiling by RT-PCR of 12 genes (8 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence risk score) to line 191 CANCER OF BREAST; AT HIGH RISK OF BREAST CANCER
        2. Modify Guideline Note 148 as shown below
e. Decipher for prostate cancer
    i. CPT **81542** Oncology (prostate), mRNA, microarray gene expression profiling of 22 content genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as metastasis risk score
    ii. Description: CPT 81542 appears to represent a test known as Decipher. Prostate cancer algorithmic tests were reviewed in an HTAS coverage guidance in January, 2018. All prostate cancer algorithmic testing, including Decipher, was reviewed, and given a strong recommendation for non-coverage.
    iii. <u>HERC staff recommendation</u>
        1. Add CPT **81542** (Oncology (prostate), mRNA, microarray gene expression profiling of 22 content genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as metastasis risk score) to line 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
        2. Modify Guideline Note 148 as shown below
        3. Add an entry to Guideline Note 173 as shown below
f. Gene expression profiling for uveal melanoma
    i. CPT **81552** Oncology (uveal melanoma), mRNA, gene expression profiling by real-time RT-PCR of 15 genes (12 content and 3 housekeeping), utilizing fine needle aspirate or formalin-fixed paraffin-embedded tissue, algorithm reported as risk of metastasis
    ii. Uveal melanoma is a rare disease of the eye that has a different prognosis and treatment than cutaneous melanoma. CPT 81552 represents DecisionDX, a gene expression profile that determines the molecular signature of a patient's melanoma. The results of the test provide knowledge regarding the risk of near-term metastasis (5 years). Tumors with a Class 1 signature are associated with a good prognosis and a low potential to metastasize, while tumors with a Class 2 signature have a high potential to spread.
    iii. Uveal melanoma (ICD10 C69.9) is on line 113 CANCER OF EYE AND ORBIT
    iv. **NCCN** 1.2019 Uveal Melanoma
        1. Footnote: “Biopsy of primary tumor does not improve outcomes, but may provide prognostic information that can help inform frequency of

follow up and may be needed for eligibility for clinical trials. Specimen should be sent for cytology, chromosome analysis, and/or gene expression profiling. The risks/benefits of biopsy for prognostic analysis should be carefully considered and discussed."

v. Other guidelines
    1. **Nathan 2015**, UK guideline for uveal melanoma (approved by NICE)
        a. Consider collecting molecular genetic and/or cytogenetic data for research and prognostication purposes where tumour material is available and where patient consent has been obtained as part of an ethically approved research programme. [GPP—expert opinion]

vi. HERC staff summary: gene expression profiling does not have adequate evidence that the test affects clinical outcomes. It is mentioned in the NCCN guideline for uveal melanoma, but only as an option if a biopsy is done. A trusted source (NICE) recommends only as part of a research trial.

vii. <u>HERC staff recommendation</u>
    1. Add CPT **81552** (Oncology (uveal melanoma), mRNA, gene expression profiling by real-time RT-PCR of 15 genes (12 content and 3 housekeeping), utilizing fine needle aspirate or formalin-fixed paraffin-embedded tissue, algorithm reported as risk of metastasis) to line 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
    2. Modify GN173 as shown below

GUIDELINE NOTE 148, BIOMARKER TESTS OF CANCER TISSUE

Lines 157,184,191,230,263,271,329

The use of tissue of origin testing (e.g. CPT 81504) is included on Line 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS.

For early stage breast cancer, the following breast cancer genome profile tests are included on Line 191 when the listed criteria are met. One test per primary breast cancer is covered when the patient is willing to use the test results in a shared decision-making process regarding adjuvant chemotherapy. Lymph nodes with micrometastases less than 2 mm in size are considered node negative.

- Oncotype DX Breast Recurrence Score (CPT 81519) for breast tumors that are estrogen receptor positive, HER2 negative, and either lymph node negative, or lymph node positive with 1-3 involved nodes.
- EndoPredict (~~using~~ CPT ~~81599~~ <u>81522</u>) and Prosigna (CPT 81520 or PLA 0008M) for breast tumors that are estrogen receptor positive, HER2 negative, and lymph node negative.
- MammaPrint (using CPT 81521 or HCPCS S3854) for breast tumors that are estrogen receptor or progesterone receptor positive, HER2 negative, lymph node negative, and only in those cases categorized as high clinical risk.

EndoPredict, Prosigna, and MammaPrint are not included on Line 191 for early stage breast cancer with involved axillary lymph nodes. Oncotype DX Breast Recurrence Score is not included on Line 191 for breast cancer involving four or more axillary lymph nodes or more extensive metastatic disease.

Oncotype DX Breast DCIS Score (CPT 81479) and Breast Cancer Index (CPT 81518) are included on Line 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS.

For melanoma, BRAF gene mutation testing (CPT 81210) is included on Line 230.

For lung cancer, epidermal growth factor receptor (EGFR) gene mutation testing (CPT 81235) is included on Line 263 only for non-small cell lung cancer. KRAS gene mutation testing (CPT 81275) is not included on this line.

For colorectal cancer, KRAS gene mutation testing (CPT 81275) is included on Line 157. BRAF (CPT 81210) and Oncotype DX are not included on this line. Microsatellite instability (MSI) is included on the Line 660

For bladder cancer, Urovysion testing is included on Line 660.

For prostate cancer, Oncotype DX Genomic Prostate Score, Prolaris Score Assay, and Decipher Prostate RP (CPT 81542) are included on Line 660.

The development of this guideline note was informed by a HERC coverage guidance on Biomarkers Tests of Cancer Tissue for Prognosis and Potential Response to Treatment; the prostate-related portion of that coverage guidance was superseded by a Coverage Guidance on Gene Expression Profiling for Prostate Cancer. See https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports.aspx.

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

Line 660

The following Interventions are prioritized on Line 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
81277	Cytogenomic neoplasia (genome-wide) microarray analysis, interrogation of genomic regions for copy number and loss-of-heterozygosity variants for chromosomal abnormalities	Insufficient evidence of effectiveness	November 2019
81542	Oncology (prostate), mRNA, microarray gene expression profiling of 22 content genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as metastasis risk score	Insufficient evidence of effectiveness	January 2018

81552	Oncology (uveal melanoma), mRNA, gene expression profiling by real-time RT-PCR of 15 genes (12 content and 3 housekeeping), utilizing fine needle aspirate or formalin-fixed paraffin-embedded tissue, algorithm reported as risk of metastasis	Insufficient evidence of effectiveness	November 2019

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journal homepage: www.ejcancer.com

Review

Uveal Melanoma UK National Guidelines

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KEYWORDS
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UK

Abstract The United Kingdom (UK) uveal melanoma guideline development group used an evidence based systematic approach (Scottish Intercollegiate Guidelines Network (SIGN)) to make recommendations in key areas of uncertainty in the field including: the use and effectiveness of new technologies for prognostication, the appropriate pathway for the surveillance of patients following treatment for primary uveal melanoma, the use and effectiveness of new technologies in the treatment of hepatic recurrence and the use of systemic treatments. The guidelines were sent for international peer review and have been accredited by NICE. A

This project is the independent work of the Uveal Melanoma Guideline Development Group and is funded by Melanoma Focus (http://melanomafocus.com/).

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E-mail addresses: nathan.pd@gmail.com, p.nathan@nhs.net (P. Nathan).

[1] Ms Curtis and Mr McGuirk shared attendance at GDG meeting. When neither could attend Mr Rob Cheek, another member of OcuMel board, attended. Sadly, Kieran McGuirk died in September 2014.

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summary of key recommendations is presented. The full documents are available on the Melanoma Focus website.

1. Introduction

1.1. Aim of the guideline

The aim of these guidelines is to optimise patient care by providing recommendations based on the best available scientific evidence. These guidelines should assist the planning of patient care and provide an indication of the likely clinical outcomes, as well as facilitating patient counselling and informed decision-making. Where adequate evidence is lacking, the guideline development group (GDG) has, where possible, arrived at an expert consensus. The Group recognises, however, that each patient is an individual. These guidelines should therefore neither be prescriptive nor dictate clinical care; however, where care significantly differs from the guidelines, it should be justifiable. Our review also identifies gaps in current evidence, thereby defining scope for further research and audit.

The GDG reviewed the evidence, where available, for the key areas of uncertainty in the field, which include:

- The use and effectiveness of new technologies such as cytogenetics/genetic analysis for prognostication.
- The appropriate pathway for the surveillance of patients following treatment for primary uveal melanoma.
- The use and effectiveness of new technologies in the treatment of hepatic recurrence.
- The use of systemic treatments.

1.2. Background

Uveal melanoma has an incidence of approximately 2–8 per million per year in Caucasians [23] these tumours are even less common in races with brown eyes. More than 90% involve the choroid, the remainder being confined to iris and ciliary body. Both sexes are affected in equal numbers [12,5]. The age at presentation peaks at approximately 60 years, except for iris melanomas, which usually present at a younger age [5,18]. Risk factors for uveal melanoma include light-coloured irides [15], congenital ocular melanocytosis [19], melanocytoma [14] and neurofibromatosis [19]. The role of sunlight is uncertain [20]. Familial cases are very rare but some patients may have familial atypical mole and melanoma syndrome; these cases require monitoring by a dermatologist as they are also at risk of cutaneous melanoma [22]. Rare families carry germline mutations of the BAP1 gene on chromosome 3, which predisposes them to develop uveal melanoma, mesothelioma and other cancers [2].

Staging for uveal melanoma follows the American Joint Committee on Cancer (AJCC) Tumour-Node-Metastasis (TNM) staging system for eye cancer [7,8]. Outcomes for patients with uveal melanoma vary widely, but for patients with early tumours they are excellent. In a cohort of 8033 patients, the 10-year metastatic rate for a 1-mm-thick uveal melanoma was 5%, for a 2-mm-thick uveal melanoma it was 10%, and that for a 6-mm-thick uveal melanoma it was 30% [16,17]. When grouping 7621 uveal melanomas into small (0–3 mm thick, 29.8%), medium (3.1–8 mm thick, 49%) or large (>8 mm thick, 20.9%) tumours, the 10-year rates of detecting metastases were 11.5%, 25.5% and 49.2% respectively [16,17].

An online tool, the Liverpool Uveal Melanoma Prognosticator Online (LUMPO), has been developed and is freely available. It generates an all-cause mortality curve according to age, sex, AJCC TNM size category (based on basal tumour diameter and tumour height), ciliary body involvement, melanoma cytomorphology, closed loops, mitotic count, chromosome 3 loss and presence of extraocular spread (www.ocularmelanomaonline.com) [4].

Cytogenetic and molecular genetic features of the uveal cells have been demonstrated to have strong prognostication value in uveal melanoma. The most striking abnormality in uveal melanoma is the complete or partial loss of chromosome 3. Other common genetic abnormalities of uveal melanoma include loss on the short arm (p) of chromosome 1, and gains on 6p and 8q (see review, [3]. The above-mentioned chromosomal alterations in primary UM are clinically relevant because of their correlation with the risk of metastatic death. Chromosome 3 loss is associated with a reduction of the 5-year survival probability from approximately 100% to about 50%. Similarly, chromosome 8 gains and loss of chromosome 1 significantly correlate with reduced survival [21,13]. Conversely, gains in chromosome 6p correlate with a good prognosis, suggesting this aberration may have a functionally protective effect.

The natural history of uveal melanoma is characterised by the frequent development of metastases and patients develop metastatic disease at any time from the initial diagnosis of the primary to several decades later [9,6,11]. The risk of metastatic relapse for an individual varies greatly dependent on primary tumour characteristics and genetic alterations.

Section 4.0

Non-Prenatal Non-Cancer Genetic Testing

Non-Prenatal, Non-Cancer Genetic Testing Guideline

Issue: Several changes are suggested by HERC staff for GAP consideration for the Diagnostic Guideline D1.

1) Changes based on the Cytochrome P450 review (separate document)
    a. Add an entry for CPT 81226 to specify that it is only covered for patients being considered for eliglustat or tetrabenazine therapy
    b. Add an entry for CPT 81227 to clarify that it is only covered for patients being considered for siponimod therapy for MS
2) Consider changes to the entry for microarray analysis (CPT 81228 and 81229)
    a. From CareOregon: Could we please discuss 81228 and 81229, both microarrays for deletions and duplications, but 81229 includes SNPs. GN D1 places some restrictions on 81229, but in speaking with the genetics counselors and some of the labs, it seems 81229 has largely replaced 81228- in fact, some labs claim they no longer run 81228 arrays. Would like clarification on this.
3) Consider clarification for whole exome sequencing coverage (CPT 81415 and 81416)
    a. From CareOregon: Would also like some clarification on whole exome sequencing (WES) in the era of next-generation sequencing, with very rare requests for Sanger sequence of individual genes. There are a lot of labs offering this test, however the Legacy group has a preference for GeneDx, which can be very expensive (I was quoted $25K for a whole exome, $19,300 for a nystagmus panel, which is just a 825 gene subset of a whole genome). It would be nice to have some agreed-on pricing on whole exome, and clarification for condition-specific subsets. I think some labs offer WES in the $5K range, but they are not all of similar precision. Also would appreciate some guidance on "Trio" WES, which includes both parents to help interpret the significance of mutations identified in the proband. Seems to be used when a mutation is suspected, but does not fit a named syndrome.
    b. Reviewed as a new code in 2014, added as diagnostic with required genetic counseling prior to testing
    c. NOTE: Washington HTA is currently conducting an evidence review on WES, with a final draft due October 22, 2019. Staff recommendation is to wait for the final WA HTA report, and either readdress this topic at the 2020 GAP meeting or at a future VbBS meeting

DIAGNOSTIC GUIDELINE D1, NON-PRENATAL GENETIC TESTING GUIDELINE

A) Genetic tests are covered as diagnostic, unless they are listed below in section E1 as excluded or have other restrictions listed in this guideline. To be covered, initial screening (e.g. physical exam, medical history, family history, laboratory studies, imaging studies) must indicate that the chance of genetic abnormality is > 10% and results would do at least one of the following:
    1) Change treatment,
    2) Change health monitoring,
    3) Provide prognosis, or
    4) Provide information needed for genetic counseling for patient; or patient's parents, siblings, or children
B) Pretest and posttest genetic counseling is required for presymptomatic and predisposition genetic testing. Pretest and posttest genetic evaluation (which includes genetic counseling) is

covered when provided by a suitable trained health professional with expertise and experience in genetics.

1) "Suitably trained" is defined as board certified or active candidate status from the American Board of Medical Genetics, American Board of Genetic Counseling, or Genetic Nursing Credentialing Commission.

C) A more expensive genetic test (generally one with a wider scope or more detailed testing) is not covered if a cheaper (smaller scope) test is available and has, in this clinical context, a substantially similar sensitivity. For example, do not cover CFTR gene sequencing as the first test in a person of Northern European Caucasian ancestry because the gene panels are less expensive and provide substantially similar sensitivity in that context Related to diagnostic evaluation of individuals with intellectual disability (defined as a full scale or verbal IQ < 70 in an individual > age 5), developmental delay (defined as a cognitive index <70 on a standardized test appropriate for children < 5 years of age), Autism Spectrum Disorder, or multiple congenital anomalies:

1) CPT 81228, Cytogenomic constitutional microarray analysis for copy number variants for chromosomal abnormalities: Cover for diagnostic evaluation of individuals with intellectual disability/developmental delay; multiple congenital anomalies; or, Autism Spectrum Disorder accompanied by at least one of the following: dysmorphic features including macro or microcephaly, congenital anomalies, or intellectual disability/developmental delay in addition to those required to diagnose Autism Spectrum Disorder.
2) CPT 81229, Cytogenomic constitutional microarray analysis for copy number variants for chromosomal abnormalities; plus cytogenetic constitutional microarray analysis for single nucleotide polymorphism (SNP) variants for chromosomal abnormalities: Cover for diagnostic evaluation of individuals with intellectual disability/developmental delay; multiple congenital anomalies; or, Autism Spectrum Disorder accompanied by at least one of the following: dysmorphic features including macro or microcephaly, congenital anomalies, or intellectual disability/developmental delay in addition to those required to diagnose Autism Spectrum Disorder; only if (a) consanguinity and recessive disease is suspected, or (b) uniparental disomy is suspected, or (c) another mechanism is suspected that is not detected by the copy number variant test alone.
3) CPT 81243, 81244, 81171,81172 Fragile X genetic testing is covered for individuals with intellectual disability/developmental delay. Although the yield of Fragile X is 3.5-10%, this is included because of additional reproductive implications.
4) A visit with the appropriate specialist (often genetics, developmental pediatrics, or child neurology), including physical exam, medical history, and family history is covered. Physical exam, medical history, and family history by the appropriate specialist, prior to any genetic testing is often the most cost-effective strategy and is encouraged.

D) Related to other tests with specific CPT codes:

1) Certain genetic tests have not been found to have proven clinical benefit. These tests are listed in Guideline Note 173, INTERVENTIONS THAT HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS; UNPROVEN INTERVENTIONS
2) The following tests are covered only if they meet the criteria in section A above AND the specified situations:
    a) CPT 81205, BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide) (eg, Maple syrup urine disease) gene analysis, common variants (eg, R183P, G278S,

E422X): Cover only when the newborn screening test is abnormal and serum amino acids are normal

b) Diagnostic testing for cystic fibrosis (CF)
   i) CFTR, cystic fibrosis transmembrane conductance regulator tests. CPT 81220, 81222, 81223: For infants with a positive newborn screen for cystic fibrosis or who are symptomatic for cystic fibrosis, or for clients that have previously been diagnosed with cystic fibrosis but have not had genetic testing, CFTR gene analysis of a panel containing at least the mutations recommended by the American College of Medical Genetics* (CPT 81220) is covered. If two mutations are not identified, CFTR full gene sequencing (CPT 81223) is covered. If two mutations are still not identified, duplication/deletion testing (CPT 81222) is covered. These tests may be ordered as reflex testing on the same specimen.
c) Carrier testing for cystic fibrosis
   i) CFTR gene analysis of a panel containing at least the mutations recommended by the American College of Medical Genetics* (CPT 81220) is covered once in a lifetime.
d) CPT 81224, CFTR (cystic fibrosis transmembrane conductance regulator) (eg. cystic fibrosis) gene analysis; introm 8 poly-T analysis (eg. male infertility): Covered only after genetic counseling.
e) CPT 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)). Covered only for determining eligibility for eliglustat or tetrabenazine therapy
f) CPT 81227, CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6). Covered only for determining eligibility for siponimod therapy for multiple sclerosis.
g) CPT 81240. F2 (prothrombin, coagulation factor II) (eg, hereditary hypercoagulability) gene analysis, 20210G>A variant: Factor 2 20210G>A testing should not be covered for adults with idiopathic venous thromoboembolism; for asymptomatic family members of patients with venous thromboembolism and a Factor V Leiden or Prothrombin 20210G>A mutation; or for determining the etiology of recurrent fetal loss or placental abruption.
h) CPT 81241. F5 (coagulation Factor V) (eg, hereditary hypercoagulability) gene analysis, Leiden variant: Factor V Leiden testing should not be covered for: adults with idiopathic venous thromoboembolism; for asymptomatic family members of patients with venous thromboembolism and a Factor V Leiden or Prothrombin 20210G>A mutation; or for determining the etiology of recurrent fetal loss or placental abruption.
i) CPT 81247. G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; common variant(s) (eg, A, A-) should only be covered
   i) After G6PD enzyme activity testing is done and found to be normal; AND either
      (a) There is an urgent clinical reason to know if a deficiency is present, e.g. in a case of acute hemolysis; OR
      (b) In situations where the enzyme activity could be unreliable, e.g. female carrier with extreme Lyonization.
j) CPT 81248. G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; known familial variant(s) is only covered when the information is required for genetic counseling.

k) CPT 81249. G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; full gene sequence is only covered
    i) after G6PD enzyme activity has been tested, and
    ii) the requirements under CPT 81247 above have been met, and
    iii) common variants (CPT 81247) have been tested for and not found.
l) CPT 81256, HFE (hemochromatosis) (eg, hereditary hemochromatosis) gene analysis, common variants (eg, C282Y, H63D): Covered for diagnostic testing of patients with elevated transferrin saturation or ferritin levels. Covered for predictive testing ONLY when a first degree family member has treatable iron overload from HFE.
m) CPT 81332, SERPINA1 (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1) (eg, alpha-1-antitrypsin deficiency), gene analysis, common variants (eg, *S and *Z): The alpha-1-antitrypsin protein level should be the first line test for a suspected diagnosis of AAT deficiency in symptomatic individuals with unexplained liver disease or obstructive lung disease that is not asthma or in a middle age individual with unexplained dyspnea. Genetic testing of the anpha-1 phenotype test is appropriate if the protein test is abnormal or borderline. The genetic test is appropriate for siblings of people with AAT deficiency regardless of the AAT protein test results.
n) CPT 81329, Screening for spinal muscular atrophy: is covered once in a lifetime for preconception testing or testing of the male partner of a pregnant female carrier
o) CPT 81415-81416, exome testing: A genetic counseling/geneticist consultation is required prior to ordering test
p) CPT 81430-81431, Hearing loss (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); genomic sequence analysis panel: Testing for mutations in GJB2 and GJB6 need to be done first and be negative in non-syndromic patients prior to panel testing.
q) CPT 81440, 81460, 81465, mitochondrial genome testing: A genetic counseling/geneticist or metabolic consultation is required prior to ordering test.
r) CPT 81412 Ashkenazi Jewish carrier testing panel: panel testing is only covered when the panel would replace and would be similar or lower cost than individual gene testing including CF carrier testing.

* American College of Medical Genetics Standards and Guidelines for Clinical Genetics Laboratories. 2008 Edition, Revised 7/2018 and found at http://www.acmg.net/PDFLibrary/Cystic-Fibrosis-Population-Based-Carrier-Screening-Standards.pdf.

Cytochrome P450 Genetic Testing Indications

Questions:

1) Should CYP2C9 genetic testing be paired with any diagnoses other than multiple sclerosis?
2) Should any other cytochrome P450 genetic tests be covered for any diagnosis?

Question source: HERC; HERC staff

Issues: Recently, the FDA approved siponimod (brand name Mayzent) as a new medication for multiple sclerosis (MS), but required CYP2C9*3/*3 genetic testing prior to prescribing. If a patient is positive for the CYP2C9*3/*3 genetic variant, the drug is contraindicated.

Testing is billed with CPT 81227 (CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6)), which is currently on line 660/GN173. CPT 81227 was placed on line 660 as a new 2012 CPT code. At the time of the 2011 Genetics Advisory Panel review, this code was being used for testing for determining anticoagulant therapy, for which there is no evidence of effectiveness.

At the August, 2019 HERC meeting, CPT 81227 was added to the MS line and deleted from Line 660 to allow testing prior to siponimod therapy. The HERC requested that the GAP provide input into any additional indications/diagnoses that should be paired with CPT 81227.

Review of commercial payer coverage policies found no other indications for CPT 81227 that are currently covered.

Additionally, there are multiple other cytochrome P450 genetic tests for drug metabolism which are all currently non-covered. These were reviewed as new CPT codes in 2011 and 2017, and found to have no evidence of effectiveness.

1) CPT 81225 (CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *8, *17)) is covered by some private insurers for testing prior to initiation of clopidogrel
2) CPT 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)) is covered by some private insurers for testing prior to tetrabenazine or eliglustat therapy. We have received a request from the Pharmacy and Therapeutics Committee to add coverage for this test for patients being considered for eliglustat therapy due to the drug being contraindicated in patients with certain mutations. P&T staff also recommend adding coverage for patients being considered for tetrabenazine therapy for Huntington's disease, as the FDA labeling recommends testing for mutations prior to giving doses greater than 50mg
3) CPT 81230 (CYP3A4 (cytochrome P450 family 3 subfamily A member 4) (eg, drug metabolism), gene analysis, common variant(s) (eg, *2, *22)) does not appear to be covered by private insurers
4) CPT 81231 (CYP3A5 (cytochrome P450 family 3 subfamily A member 5) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *7)) does not appear to be covered by private insurers

HERC staff recommendations:

1) Do not add CPT 81227 (CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6)) to any additional lines on the Prioritized List
2) Remove CPT 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)) from line 660/GN173
    a. Advise HSD to add CPT 81226 to the Diagnostic File
3) Add the following entries to section D of DIAGNOSTIC GUIDELINE D1, NON-PRENATAL GENETIC TESTING GUIDELINE
    a. CPT 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)). Covered only for determining eligibility for eliglustat or tetrabenazine therapy
    b. CPT 81227, CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6). Covered only for determining eligibility for siponimod therapy for multiple sclerosis.
4) Do not add coverage for other cytochrome P450 gene testing
5) Revise GN173 to have two entries for cytochrome P450 gene analysis to clarify review dates

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

Line 660

The following Interventions are prioritized on Line 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
~~81225,81226, 81230-81231~~	~~Cytochrome P450 gene analysis~~	~~Insufficient evidence of effectiveness~~	~~December, 2011~~ ~~November, 2017~~
81225	Cytochrome P450 family 2 subfamily 3 gene analysis	Insufficient evidence of effectiveness	November 2019
81230-81231	Cytochrome P450 family 3 gene analysis	Insufficient evidence of effectiveness	November 2019

Section 5.0

Prenatal Genetic Testing

Prenatal Genetic Testing Guideline

Issue: Several changes are recommended by HERC staff for GAP consideration

1) Follow up from the 2018 GAP meeting
    a. Delete screening for thrombophilia from the guideline
        i. Does not refer to a prenatal test
2) Include only the ACOG recommended CF testing CPT code (81220)
    a. 81220: CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)
    b. See separate cystic fibrosis screening summary

DIAGNOSTIC GUIDELINE D17, PRENATAL GENETIC TESTING

The following types of prenatal genetic testing and genetic counseling are covered for pregnant women:

A) Genetic counseling (CPT 96040, HPCPS S0265) for high-risk women who have family history of inheritable disorder or carrier state, ultrasound abnormality, previous pregnancy with aneuploidy, or elevated risk of neural tube defect.
B) Genetic counseling (CPT 96040, HPCPS S0265) prior to consideration of chorionic villus sampling (CVS), amniocentesis, microarray testing, Fragile X, and spinal muscular atrophy screening
C) Validated questionnaire to assess genetic risk in all pregnant women
D) Screening high-risk ethnic groups for hemoglobinopathies (CPT 83020, 83021)
E) Screening for aneuploidy with any of five screening strategies [first trimester (nuchal translucency, beta-HCG and PAPP-A), integrated, serum integrated, stepwise sequential, and contingency] (CPT 76813, 76814, 81508-81511,81512,82105,82677)
F) Cell free fetal DNA testing (CPT 81420, 81507) for evaluation of aneuploidy in women who have an elevated risk of a fetus with aneuploidy (maternal age >34, family history or elevated risk based on screening).
G) Ultrasound for structural anomalies between 18 and 20 weeks gestation (CPT 76811, 76812)
H) CVS or amniocentesis (CPT 59000, 59015, 76945,76946, 82106, 88235, 88261-88264, 88267, 88269, 88280, 88283, 88285, 88289,88291) for a positive aneuploidy screen, maternal age >34, fetal structural anomalies, family history of inheritable chromosomal disorder or elevated risk of neural tube defect.
I) Array CGH (CPT 81228, 81229) when major fetal congenital anomalies are apparent on imaging, or with normal imaging when array CGH would replace karyotyping performed with CVS or amniocentesis in #8 above.
J) FISH testing (CPT 88271, 88272, 88274, 88275, 81171, 81172) only if karyotyping is not possible due a need for rapid turnaround for reasons of reproductive decision-making (i.e. at 22w4d gestation or beyond)
K) Screening for Tay-Sachs carrier status (CPT 81255) in high-risk populations. First step is hex A, and then additional DNA analysis in individuals with ambiguous Hex A test results, suspected variant form of TSD or suspected pseudodeficiency of Hex A
L) Screening for cystic fibrosis carrier status once in a lifetime (CPT 81220~~-81224~~)
M) Screening for fragile X status (CPT 81243, 81244, 81171. 81172) in patients with a personal or family history of

    a. fragile X tremor/ataxia syndrome
    b. premature ovarian failure
    c. unexplained early onset intellectual disability
    d. fragile X intellectual disability
    e. unexplained autism through the pregnant woman's maternal line
N) Screening for spinal muscular atrophy (CPT 81239) once in a lifetime
O) Screening those with Ashkenazi Jewish heritage for Canavan disease (CPT 81200), familial dysautonomia (CPT 81260), and Tay-Sachs carrier status (CPT 81255). Ashkenazi Jewish carrier panel testing (CPT 81412) is covered if the panel would replace and would be of similar or lower cost than individual gene testing including CF carrier testing.
P) Expanded carrier screening only for those genetic conditions identified above

The following genetic screening tests are not covered:

A) Serum triple screen
B) ~~Screening for thrombophilia in the general population or for recurrent pregnancy loss~~
C) Expanded carrier screening which includes results for conditions not explicitly recommended for coverage

The development of this guideline note was informed by a HERC coverage guidance. See https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports.aspx.

Cystic Fibrosis Genetic Testing Guideline Inconsistency

Issue: the entry for genetic testing for cystic fibrosis in the prenatal genetic testing guideline is different from the entry for cystic fibrosis testing in the non-prenatal, non-cancer genetic testing guideline. Additionally, the non-prenatal genetic testing guideline has several entries for CF testing, which is confusing. PacificSource is requesting clarification on why these entries are different, and whether the GAP/HERC intends for more liberal testing for those with no symptoms of CF vs those with symptoms, which is how they are interpreting the current guideline wording.

On review, HERC staff also identified that CPT 81221 is not included in the non-prenatal genetic testing guideline for unclear reasons.

DIAGNOSTIC GUIDELINE D1, NON-PRENATAL GENETIC TESTING GUIDELINE

b) Diagnostic testing for cystic fibrosis (CF)
   i) CFTR, cystic fibrosis transmembrane conductance regulator tests. CPT 81220, 81222, 81223: For infants with a positive newborn screen for cystic fibrosis or who are symptomatic for cystic fibrosis, or for clients that have previously been diagnosed with cystic fibrosis but have not had genetic testing, CFTR gene analysis of a panel containing at least the mutations recommended by the American College of Medical Genetics* (CPT 81220) is covered. If two mutations are not identified, CFTR full gene sequencing (CPT 81223) is covered. If two mutations are still not identified, duplication/deletion testing (CPT 81222) is covered. These tests may be ordered as reflex testing on the same specimen.
c) Carrier testing for cystic fibrosis
   i) CFTR gene analysis of a panel containing at least the mutations recommended by the American College of Medical Genetics* (CPT 81220) is covered once in a lifetime
d) CPT 81224, CFTR (cystic fibrosis transmembrane conductance regulator) (eg. cystic fibrosis) gene analysis; introm 8 poly-T analysis (eg. male infertility): Covered only after genetic counseling.

DIAGNOSTIC GUIDELINE D17, PRENATAL GENETIC TESTING

L) Screening for cystic fibrosis carrier status once in a lifetime (CPT 81220-81224)

CPT code	Code description
81220	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)
81221	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; known familial variants
81222	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; duplication/deletion variants
81223	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; full gene sequence
81224	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; intron 8 poly-T analysis (eg, male infertility)

HERC staff recommendations

1) Consider adding an entry for CPT 81221 coverage in DIAGNOSTIC GUIDELINE D1, NON-PRENATAL GENETIC TESTING GUIDELINE
2) Modify DIAGNOSTIC GUIDELINE D17, PRENATAL GENETIC TESTING to only include the ACOG recommended genetic testing CPT code 81220 as shown below

DIAGNOSTIC GUIDELINE D17, PRENATAL GENETIC TESTING

L) Screening for cystic fibrosis carrier status once in a lifetime (CPT 81220~~-81224~~)

Section 6.0

Hereditary Cancer Genetic Testing

Hereditary Cancer Genetic Testing Guideline 2019

Issue: Several changes are recommended by HERC staff for GAP consideration

1) Update NCCN references as shown below
2) Consider changes based on PacificSource questions regarding the last clause in the guideline: "Hereditary breast cancer-related disorders genomic sequence analysis panels (CPT 81432, 81433, 81479) are only included for patients meeting the criteria for hereditary cancer syndrome testing per NCCN guidelines"
    a. Does this mean that a panel must only include genes associated with a specific cancer syndrome that is also mentioned in NCCN with specific testing criteria or can moderate penetrance genes be included? (Would panels with only BRCA1/2, TP53 and PTEN be covered or could panels include other genes such as PALB2, CHEK2, etc.)
    b. Would an entire panel be covered if a patient met criteria for ANY single gene in NCCN?
    c. If a moderate penetrance breast cancer gene (PALB2, CHEK2), for which no NCCN testing criteria exists is ordered as a single gene test, can this be covered, or should this be denied?

DIAGNOSTIC GUIDELINE D25, HEREDITARY CANCER GENETIC TESTING

Related to genetic testing for patients with breast/ovarian and colon/endometrial cancer or other related cancers suspected to be hereditary, or patients at increased risk to due to family history, services are provided according to the Comprehensive Cancer Network Guidelines.

A) Lynch syndrome (hereditary colorectal, endometrial and other cancers associated with Lynch syndrome) services (CPT 81288, 81292-81300, 81317-81319, 81435, 81436) and familial adenomatous polyposis (FAP) services (CPT 81201-81203) should be provided as defined by the NCCN Clinical Practice Guidelines in Oncology. Genetic/Familial High-Risk Assessment: Colorectal V2.2019 (8/8/19) ~~V1.2018 (7/12/18~~). www.nccn.org.

B) Breast and ovarian cancer syndrome genetic testing services (CPT 81162-81167, 81212, 81215-81217) for patients without a personal history of breast, ovarian and other associated cancers should be provided to high-risk patients as defined by the US Preventive Services Task Force or according to the NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast and Ovarian. V3.2019 (1/18/19) ~~V2.2019 (7/30/18).~~ www.nccn.org.

C) Breast and ovarian cancer syndrome genetic testing services (CPT 81162-81167, 81212, 81215-81217)) for women with a personal history of breast, ovarian, or other associated cancers and for men with breast or other associated cancers should be provided according to the NCCN Clinical Practice Guidelines in Oncology. Genetic/Familial High-Risk Assessment: Breast and Ovarian. V3.2019 (1/18/19) ~~V2.2019 (7/30/18).~~ www.nccn.org.

D) PTEN (Cowden syndrome) services (CPT 81321-81323) should be provided as defined by the NCCN Clinical Practice Guidelines in Oncology. Genetic/Familial High-Risk Assessment: Breast and Ovarian. V3.2019 (1/18/19) ~~V2.2019 (7/30/18)~~ or Genetic/Familial High-Risk Assessment: Colorectal V2.2019 (8/8/19) ~~V1.2018 (7/12/18).~~ www.nccn.org.

Genetic counseling should precede genetic testing for hereditary cancer whenever possible.

A) Pre and post-test genetic counseling should be covered when provided by a suitable trained health professional with expertise and experience in cancer genetics. Genetic counseling is recommended for cancer survivors when test results would affect cancer screening.
    1) "Suitably trained" is defined as board certified or active candidate status from the American Board of Medical Genetics, American Board of Genetic Counseling, or Genetic Nursing Credentialing Commission.
B) If timely pre-test genetic counseling is not possible for time-sensitive cases, appropriate genetic testing accompanied by pre- and post- test informed consent and post-test disclosure performed by a board-certified physician with experience in cancer genetics should be covered.
    1) Post-test genetic counseling should be performed as soon as is practical.

If the mutation in the family is known, only the test for that mutation is covered. For example, if a mutation for BRCA 1 has been identified in a family, a single site mutation analysis for that mutation is covered (CPT 81215), while a full sequence BRCA 1 and 2 (CPT 81163) analyses is not. There is one exception, for individuals of Ashkenazi Jewish ancestry with a known mutation in the family, the panel for Ashkenazi Jewish BRCA mutations is covered (CPT 81212).

Costs for rush genetic testing for hereditary breast/ovarian and colon/endometrial cancer is not covered.

Hereditary breast cancer-related disorders genomic sequence analysis panels (CPT 81432, 81433, 81479) are only included for patients meeting the criteria for hereditary cancer syndrome testing per NCCN guidelines.

CALR Genetic Testing for Myeloproliferative Disease

Question: Should testing for CALR be covered for patients with myeloproliferative disorders?

Question source: Holly Jo Hodges, CCO medical director

Issue: CPT 81219 (CALR (calreticulin) (eg, myeloproliferative disorders), gene analysis, common variants in exon 9) was reviewed as a new CPT code in 2015 and placed in the Services Recommended for Non-Coverage Table, as at that time it was not recommended by NCCN for work up of myeloproliferative disease. It is currently listed in the Excluded File.

Newer NCCN guidelines now recommend that patients with suspicion of myeloproliferative disease who are JAK2 V617F negative are either 1) tested for both CALR and MPL or 2) provided a multigene testing panel that includes JAK2, CALR and MPL. Testing for JAK2 (CPT 81270, JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant) is currently on the Diagnostic Procedures File.

HERC staff recommendation:

1) Advise HSD to remove CPT 81219 (CALR (calreticulin) (eg, myeloproliferative disorders), gene analysis, common variants in exon 9) from the Excluded List and add to the Diagnostic Procedures File
    a. CCOs and HSD should follow NCCN guidelines for indications for testing
    b. No changes needed to the cancer genetic testing guideline