2026 Genetic Testing Clinical Guidelines for Medical Necessity Review

Effective July 1, 2026 – January 1, 2027

Guidelines for Clinical Review Determination

Preamble

Evolent is committed to the philosophy of supporting safe and effective treatment for patients. The medical necessity criteria that follow are guidelines for the provision of diagnostic imaging. These criteria are designed to guide both providers and reviewers to the most appropriate diagnostic tests based on a patient's unique circumstances. In all cases, clinical judgment consistent with the standards of good medical practice will be used when applying the guidelines. Determinations are made based on both the guideline and clinical information provided at the time of the request. It is expected that medical necessity decisions may change as new evidence-based information is provided or based on unique aspects of the patient's condition. The treating clinician has final authority and responsibility for treatment decisions regarding the care of the patient.

Guideline Development Process

These medical necessity criteria were developed by Evolent for the purpose of making clinical review determinations for requests for therapies and diagnostic procedures. The developers of the criteria sets included representatives from the disciplines of radiology, internal medicine, nursing, cardiology, and other specialty groups. Evolent's guidelines are reviewed yearly and modified when necessary following a literature search of pertinent and established clinical guidelines and accepted diagnostic imaging practices.

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Autism Spectrum Disorder/Intellectual Disability Panel Analysis

1. The use of an autism spectrum disorder/intellectual disability panel is considered **investigational** for all indications.

Rationale and References

Concert Evidence Review for Coverage Determination for Cancer Exome And Genome Sequencing. Published 06/01/2025.

This review focused on a search for evidence-based guidelines and peer-reviewed, published evidence of the clinical validity and utility of autism spectrum disorder/intellectual disability multigene panel tests. The review was limited to literature published between 05/21/2024 to 05/21/2025. A total of 112 abstracts were identified and 7 full text publications were fully reviewed, none of which met the inclusion criteria.

There were no new guidelines identified and no peer-reviewed literature identified to include in the evidence review.

There is INSUFFICIENT EVIDENCE in published guidelines and peer-reviewed literature to definitively demonstrate improved health outcomes from the use of autism spectrum disorder/intellectual disability multigene panel tests, as compared to the current standard of care. At this time, the available evidence does not support health plan coverage of these tests compared to other, guideline-supported testing methodologies.

Definitions

1. **Autism spectrum disorder** is defined in the DSM V as persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history:
   1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.

2. Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.
3. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.

2. **Intellectual disability (ID)** is defined by the DSM V as an individual age 5 or older with either an IQ score of 70 or below, OR with a clinical diagnosis of intellectual disability per the DSM V, which includes all of the following:
    1. Deficits in intellectual functions, such as reasoning, problem solving, planning, abstract thinking, judgment, academic learning, and learning from experience, confirmed by both clinical assessment and individualized, standardized intelligence testing.
    2. Deficits in adaptive functioning that result in failure to meet developmental and sociocultural standards for personal independence and social responsibility. Without ongoing support, the adaptive deficits limit functioning in one or more activities of daily life, such as communication, social participation, and independent living, across multiple environments, such as home, school, work, and community.
    3. Onset of intellectual and adaptive deficits during the developmental period.

Bladder Cancer Treatment and Recurrence Algorithmic Tests

1. The use of bladder cancer treatment and recurrence algorithmic test is considered **medically necessary** when:

    1. The member has a diagnosis of bladder cancer, **AND**

    2. The results of algorithmic testing will affect management decisions for the member's bladder cancer, **AND**

    3. The member has not previously undergone bladder cancer treatment and recurrence algorithmic testing for the current cancer diagnosis.

2. The use of bladder cancer treatment and recurrence algorithmic test is considered **investigational** for all other indications.

Rationale and References

Centers for Medicare & Medicaid Services. Medicare Coverage Database: Local Coverage Determination. MolDX: Prognostic and Predictive Molecular Classifiers for Bladder Cancer (L38576). Effective 07/18/2021. Updated 07/03/2025. Available at: https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=38576

The CMS local coverage determination (LCD) entitled "MolDX: Prognostic and Predictive Molecular Classifiers for Bladder Cancer" states the following regarding bladder cancer molecular diagnostic tests, including algorithmic tests: "This contractor will cover molecular diagnostic tests for use in a beneficiary with bladder cancer when all of the following conditions are met: The beneficiary is being actively managed for bladder cancer. At least 1 of the 2 criteria are met: The patient is a candidate for multiple potential treatments, which could be considered to have varied or increasing levels of intensity based on a consensus guideline, and the physician and patient must decide among these treatments. OR The patient is a candidate for multiple therapies, and the test has shown that it predicts response to a specific therapy among accepted therapy options based on nationally recognized society consensus guidelines The test successfully completes a Molecular Diagnostic Services Program (MolDX) technical assessment

that ensures the test is reasonable and necessary as described above. Only 1 test may be performed prior to the initiation of therapy UNLESS a second test that interrogates different genomic content AND meets all the criteria established herein, is reasonable and necessary. The genomic content interrogated by the test must be relevant to the therapy under consideration."

***National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Bladder Cancer 2.2025
https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf ***

This guideline recommends consideration of testing for urinary urothelial tumor markers in the surveillance of high risk non-muscle-invasive bladder cancer (p. BL-E 2 of 6). Of note, this is a category 2B recommendation, which NCCN defines as having lower-level evidence without uniform consensus amongst the expert panel (CAT-1).

Definitions

1. **Algorithmic test** is one that combines biomarkers and clinical data into an algorithm to generate a disease risk assessment, prognostic result, or clinical recommendation for treatment.

Breast Cancer Extended Endocrine Therapy Algorithmic Tests

1. The use of the breast cancer extended endocrine therapy test Breast Cancer Index (BCI) is considered **medically necessary** when:

    1. The member is female (sex assigned at birth), **AND**

    2. The member has primary breast cancer that is ductal/NST, lobular, mixed or micropapillary, **AND**

    3. The member's tumor is hormone receptor-positive (estrogen receptor-positive or progesterone receptor-positive), **AND**

    4. The member's tumor is human epidermal growth factor receptor 2 (HER2)-negative, **AND**

    5. The member has no distant metastases, **AND**

    6. The member has completed at least 4 years of endocrine therapy, **AND**

    7. The member is considering extended treatment with adjuvant therapy (e.g., tamoxifen, aromatase inhibitors, immunotherapy), **AND**

    8. The member meets one of the following (regardless of menopausal status):

        1. Tumor is greater than 0.5 cm and node negative (pN0), **OR**

        2. Lymph nodes are pN1mi (2 mm or smaller axillary node metastases), **OR**

        3. Lymph nodes are pN1 (1-3 positive nodes).

2. The use of the breast cancer extended endocrine therapy test Breast Cancer Index (BCI) in men (sex assigned at birth) with breast cancer is considered **investigational**.

3. The use of the breast cancer extended endocrine therapy test Breast Cancer Index (BCI) is considered **investigational** for all other indications.

Rationale and References

Andre F, Ismaila N, Allison KH, et al. Biomarkers for Adjuvant Endocrine and Chemotherapy in Early-Stage Breast Cancer: ASCO Guideline Update [published correction appears in J Clin Oncol. 2022 Aug 1;40(22):2514]. J Clin Oncol. 2022;40(16):1816-1837. doi:10.1200/JCO.22.00069

In 2022, ASCO issued a guideline regarding the use of Breast Cancer Index testing for extended endocrine therapy for ER-positive HER2-negative breast cancer. They recommend consideration of the Breast Cancer Index (BCI) test for either node-negative cancer or cancer with 1-3 positive nodes, which has been treated with primary endocrine therapy for 5 years with no evidence of recurrence (Recommendation 1.24., p. 1819).

The guideline cites a lack of sufficient evidence for the BCI test to guide decisions about extended endocrine therapy in individuals with node-positive breast cancer with 4 or more positive nodes following 5 years of endocrine therapy (Recommendation 1.25, p. 1819).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer 5.2025
https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

The BCI (Breast Cancer Index) is recommended by these guidelines for both indications of prognosis as well as predicting treatment for extended adjuvant endocrine therapy (p. BINV-N 1 of 5). Appropriate patients for this test include pre and postmenopausal women with HR positive, HER2 negative breast cancer (either ductal/NST, lobular, mixed, or micropapillary) (BINV-6, BINV-7, BINV-8).

Postmenopausal breast tumors must be one of the following: 0.5 cm or larger pN1mi (2 mm or smaller axillary node metastases) pN1 (1–3 positive nodes) (p. BINV-6, BINV-N 1 of 5).

Premenopausal tumors must be one of the following: 0.5 cm or larger and pN0 (p. BINV-7) pN1mi (2 mm or smaller axillary node metastasis) (BINV-8) pN1 (1–3 positive nodes) (BINV-8).

NCCN guidelines also state that there is limited data regarding the use of these tests in males with breast cancer who are being considered for chemotherapy (p. BINV-J 1 of 2).

Definitions

1. **Adjuvant** therapy is medication (such as chemotherapy or endocrine therapy) given after the surgical removal of a cancerous tumor.
2. **Breast cancer** is a term that applies to patients with invasive cancer or ductal carcinoma in situ (DCIS).

Breast Cancer Prognostic Algorithmic Tests

1. The use of a breast cancer prognostic algorithmic test (i.e., EndoPredict, Prosigna, MammaPrint) is considered **medically necessary** when:

    1. The member is female (sex assigned at birth), **AND**

    2. The member meets at least one of the following:

        1. Postmenopausal status, **OR**

        2. Greater than 50 years of age, **AND**

    3. The member has primary breast cancer that is ductal/NST, lobular, mixed or micropapillary, **AND**

    4. The member's tumor is estrogen receptor-positive, **AND**

    5. The member's tumor is human epidermal growth factor receptor 2 (HER2)-negative, **AND**

    6. The member is considering treatment with adjuvant therapy (e.g, tamoxifen, aromatase inhibitors, immunotherapy), **AND**

    7. The member has had axillary nodal staging and has the following node status:

        1. pN0 (nodes negative pathologically), **OR**

        2. pN1mi or pN1 (1-3 nodes positive pathologically)[1].

2. The use of a breast cancer prognostic algorithmic test (i.e., EndoPredict, Prosigna, MammaPrint) in individuals with 4 or more positive nodes is considered **investigational**.

3. The use of the breast cancer prognostic algorithmic test Prosigna in individuals with 1-3 node positive breast cancer is considered **investigational**.

4. The use of a breast cancer prognostic algorithmic test (i.e., EndoPredict, Prosigna, MammaPrint) in men (sex assigned at birth) with breast cancer is considered **investigational**.

5. The use of a breast cancer prognostic algorithmic test (i.e., EndoPredict, Prosigna, MammaPrint) is considered **investigational** for all other indications.

[1] Prosigna is indicated for node negative disease, but **not** for disease with 1-3 positive nodes. EndoPredict and Mammaprint are indicated for node negative disease and for disease with 1-3 positive nodes.

Rationale and References

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer 5.2025
https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

This guideline recommends consideration of other prognostic gene expression assays to help assess risk of recurrence in pre- and postmenopausal patients with either ductal/NST, lobular, mixed, or micropapillary breast cancer that is HR-positive, Her2-negative, pT1-3 and pN0 or pN+. However, these other tests have not been validated to predict response to chemotherapy (p. BINV- 6, BINV-7, BINV-8).

A footnote on page BINV-N 3 of 5 states: “Gene expression assays can provide prognostic and treatment-predictive information that can be used with T,N,M and biomarker information.” These prognostic gene expression assays can provide prognostic information but there is limited evidence for prediction of chemotherapy benefit (p. BINV-N 3 of 5).

Andre F, Ismaila N, Allison KH, et al. Biomarkers for Adjuvant Endocrine and Chemotherapy in Early-Stage Breast Cancer: ASCO Guideline Update [published correction appears in J Clin

Oncol. 2022 Aug 1;40(22):2514]. J Clin Oncol. 2022;40(16):1816-1837. doi:10.1200/JCO.22.00069

The 2022 ASCO guideline update for Biomarkers for Adjuvant Endocrine and Chemotherapy in Early-Stage Breast Cancer provides guidance for the diagnostic indications for several breast cancer prognostic algorithmic tests, including EndoPredict, MammaPrint, and Prosigna (among others).

Figure 1 (p. 1821) includes an algorithm that acts as a guide for prognostic test choice in women with early-stage invasive breast cancer. In summary, a female patient must have the following in order to recommend EndoPredict, Prosigna, or MammaPrint testing: Postmenopausal OR older than age 50 years Early-stage invasive breast cancer Node negative disease, HER2 negative tumor ER positive tumor

Of note, per the guide, if the patient has 1 to 3 positive node disease then only MammaPrint or EndoPredict may be ordered. The algorithm also shows that there is "Insufficient evidence to recommend a biomarker for use" in women with 4 or more positive nodes (p. 1821).

Definitions

1. **Adjuvant** therapy is medication (such as chemotherapy or endocrine therapy) given after the surgical removal of a cancerous tumor.
2. **Algorithmic test** is one that combines biomarkers and clinical data into an algorithm to generate a disease risk assessment, prognostic result, or clinical recommendation for treatment.
3. **Breast cancer** is a term that applies to patients with invasive cancer or ductal carcinoma in situ (DCIS).

Breast Cancer Treatment and Prognostic Algorithmic Tests

I. The use of the breast cancer treatment and prognostic algorithmic test Oncotype Dx Breast Recurrence Score is considered **medically necessary** in all members, regardless of gender, when:

A. The member's tumor has all of the following features:

1. Ductal/NST, lobular, mixed or micropapillary primary invasive breast cancer, **AND**

2. Hormone receptor-positive (estrogen receptor-positive or progesterone receptor-positive), **AND**

3. Human epidermal growth factor receptor 2 (HER2)-negative, **AND**

B. The member meets one of the following scenarios:

1. The member is considering neoadjuvant chemotherapy, **AND**

a) The member has no evidence of nodal involvement (cN0), **AND**

b) Breast surgery is planned, **OR**

2. The member is considering neoadjuvant chemotherapy, **AND**

a) The member is postmenopausal, **AND**

b) The member has cN1 lymph node involvement, **AND**

c) Breast surgery is planned, **OR**

3. The member is considering treatment with adjuvant therapy (e.g., tamoxifen, aromatase inhibitors, immunotherapy), **AND**

a) The member is status post tumor resection, **AND**

b) Sentinel lymph node biopsy was not performed based on preoperative risk assessment, **AND**

c) Preoperative tumor size was less than or equal to 2 cm, **AND**

d) Preoperative axillary lymph node ultrasound was negative, **OR**

4. The member is considering treatment with adjuvant therapy (e.g., tamoxifen, aromatase inhibitors, immunotherapy), **AND**

   a) The member is status post tumor resection and surgical axillary nodal staging, **AND**

   b) The member meets one of the following:

      (1) Tumor is greater than 0.5 cm and node negative (pN0), **OR**

      (2) Lymph nodes are pN1mi (2 mm or smaller axillary node metastases), **OR**

      (3) Lymph nodes are pN1 (1-3 positive nodes).

II. The use of the breast cancer treatment and prognostic algorithmic test Oncotype DX Breast Recurrence Score is considered **investigational** for all other indications.

Rationale and References

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer 1.2026
https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

Oncotype DX for breast cancer is a 21-gene expression assay and is one of many gene expression assays used to aid in determining adjuvant systemic therapy. This guideline recommends the 21-gene expression assay for both prognosis and treatment decisions in patients of either sex (p. BINV-J 1 of 2, BINV-N 1 of 5). Per NCCN, the breast tumor must be either ductal/NST, lobular, mixed, or micropapillary, and it also must be hormone receptor positive (either Estrogen receptor or Progesterone receptor), and HER2 negative (p. BINV-6, BINV-7, BINV-8).

Females (sex assigned at birth) with postmenopausal breast tumors must be considering chemotherapy and have one of the following:

- A tumor that is 0.5 cm or larger (p. BINV-6)
- A tumor that is pN1mi (2 mm or smaller axillary node metastases) (p. BINV-6)
- A tumor that is pN1 (1–3 positive nodes) (p. BINV-6).

Females (sex assigned at birth) with premenopausal breast tumors must be a candidate for chemotherapy and have one of the following:

- A tumor that is 0.5 cm or larger and pN0 (p. BINV-7)
- A tumor that is pN1mi (2 mm or smaller axillary node metastasis) (p. BINV-7)
- A tumor that is pN1 (1-3 positive nodes) (p. BINV-7).

This guideline also recommends consideration of a gene expression assay for neoadjuvant systemic therapy planning in pre or postmenopausal patients with operable ER+, HER2- breast cancer and clinically negative lymph nodes, as well as postmenopausal patients with cN1 with operable ER+, HER2- breast cancer (p. BINV-12, MS-31).

Park KU, Somerfield MR, Anne N, et al. Sentinel Lymph Node Biopsy in Early-Stage Breast Cancer: ASCO Guideline Update. J Clin Oncol. 2025;43(14):1720-1741. doi:10.1200/JCO-25-00099

This guideline states that for patients with breast cancer that is < 2 cm with a negative perioperative axillary lymph node ultrasound who meet selection criteria to avoid sentinel lymph node biopsy (SLNB), “genomic assay testing and subsequent systemic therapy decisions should not be altered by omission of SLNB in the appropriate candidates” and that the 21-gene recurrence score can be performed without an SLNB (p. 1725).

Definitions

1. **Adjuvant** therapy is medication (such as chemotherapy or endocrine therapy) given after the surgical removal of a cancerous tumor.
2. **Algorithmic test** is one that combines biomarkers and clinical data into an algorithm to generate a disease risk assessment, prognostic result, or clinical recommendation for treatment.
3. **Breast cancer** is a term that applies to patients with invasive cancer or ductal carcinoma in situ (DCIS).

Breast DCIS Prognostic Algorithmic Tests

1. Breast DCIS prognostic algorithmic tests are considered **medically necessary** when:

    1. The member has ductal carcinoma in situ (DCIS), **AND**

    2. The tumor specimen contains at least 0.5 mm of DCIS, **AND**

    3. The result of testing would aid in treatment decision-making (i.e., pursuing additional surgery or radiation therapy), **AND**

    4. The member's DCIS was not removed via mastectomy (i.e., there is residual ipsilateral breast tissue).

2. Breast DCIS prognostic algorithmic tests are considered **investigational** for all other indications.

Rationale and References

Centers for Medicare & Medicaid Services. Medicare Coverage Database: Local Coverage Local Coverage DeterminationMolDX: Oncotype DX Breast Cancer for DCIS (Genomic Health) (L36912). Effective Date 03/06/2017. Updated 11/25/2021. Available at: https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=36912

The CMS local coverage determination (LCD) entitled "MolDX: Oncotype DX Breast Cancer for DCIS (Genomic Health)" includes the following coverage criteria for OncotypeDX DCIS: "The Oncotype DX DCIS assay is covered only when the following clinical conditions are met: Pathology (excisional or core biopsy) reveals ductal carcinoma in situ of the breast (no pathological evidence of invasive disease), and FFPE specimen with at least 0.5 mm of DCIS length, and Patient is a candidate for and is considering breast conserving surgery alone as well as breast conserving surgery combined with adjuvant radiation therapy, and Test result will be used to determine treatment choice between surgery alone vs. surgery with radiation therapy, and Patient has not received and is not planning on receiving a mastectomy."

Muktar S, Kirby A, Locke I, et al. Oncotype DX Breast DCIS Score® Test: Impact on Radiotherapy Recommendations and Patient Decisional Anxiety. Clin Oncol (R Coll Radiol). 2025 Jun:42:103839. Published online April 4, 2025. doi:10.1016/j.clon.2025.103839

This single center prospective clinical trial aimed to study whether adjuvant radiation therapy recommendations would change for women with DCIS based on results of Oncotype DX Breast DCIS testing. The paper found that “in 28% of patients (20/71), the RT [radiotherapy] recommendation changed as a result of the Oncotype test, with the majority of the change being from recommending RT to omitting RT” (p. 5).

Definitions

N/A

Broad Molecular Profiling Panel Tests via Circulating Tumor DNA (ctDNA)

I. Broad molecular profiling panel tests via [circulating tumor DNA (ctDNA) are considered **medically necessary** when:

A. The member has a diagnosis, progression, or recurrence of one of the following:

1. Locally advanced/metastatic pancreatic adenocarcinoma, **OR**
2. Metastatic or advanced gastric cancer, **OR**
3. Metastatic or advanced esophageal or esophagogastric junction cancer, **OR**
4. Stage III or IV cutaneous melanoma, **OR**
5. Metastatic colorectal cancer, **OR**
6. Locally advanced or metastatic ampullary adenocarcinoma, **OR**
7. Persistent or recurrent cervical cancer, **OR**
8. Unresectable or metastatic biliary tract cancer, **OR**
9. Suspected or confirmed histiocytic neoplasm, **OR**
10. Locoregional unresectable or metastatic extrapulmonary poorly differentiated neuroendocrine neoplasms, **OR**
11. Locoregional unresectable or metastatic large or small cell neuroendocrine neoplasms, **OR**

12. Locoregional unresectable or metastatic mixed neuroendocrine-non-neuroendocrine neoplasm, **OR**

13. Suspected metastatic malignancy of unknown primary with initial determination of histology, **OR**

14. Recurrent ovarian, fallopian tube, or primary peritoneal cancer, **AND**

15. At least one of the following:

    a) The member is medically unfit for invasive tissue sampling (biopsy), **OR**

    b) Biopsy was performed, but material was insufficient for molecular analysis, **OR**

    c) Biopsy was performed, but molecular analysis was not able to be completely assessed on tissue due to availability of testing methodologies, **OR**

    d) Biopsy is not possible due to location of the tumor, **OR**

B. The member is being evaluated at diagnosis, progression, or recurrence of one of the following:

    1. Recurrent or stage IV breast cancer, **OR**

    2. Suspected or proven metastatic rectal cancer, **OR**

    3. Suspected or proven metastatic colon cancer, **OR**

    4. Locally advanced or metastatic lung adenocarcinoma, **OR**

5. Locally advanced or metastatic large cell lung carcinoma, **OR**

6. Locally advanced or metastatic squamous cell lung carcinoma, **OR**

7. Locally advanced or metastatic non-small cell lung cancer (NSCLC) not otherwise specified (NOS), **OR**

8. Locally advanced, metastatic, or recurrent small cell lung cancer, **OR**

C. The member has a diagnosis of metastatic prostate cancer, **AND**

1. The member is undergoing initial workup, **OR**

2. There is biochemical or radiologic evidence of recurrence or progression as demonstrated by either of the following:

a) Prostate specific antigen (PSA) is not undetectable, **OR**

b) There is radiographic progression.

II. Broad molecular profiling panel tests via circulating tumor DNA (ctDNA) performed simultaneously with solid tumor tissue testing is considered **medically necessary** when the member has one of the following diagnoses:

A. Lung adenocarcinoma, **OR**

B. Large cell lung carcinoma, **OR**

C. Squamous cell lung carcinoma, **OR**

D. Non-small cell lung cancer (NSCLC) not otherwise specified (NOS), **OR**

E. Locally advanced, metastatic, or recurrent small cell lung cancer.

III. Broad molecular profiling panel tests via circulating tumor DNA (ctDNA) are considered **investigational** for all other indications, including being performed simultaneously with solid tumor tissue testing for tumor types other than those described above.

Rationale and References

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Gastric Cancer 3.2025
https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf

This guideline recommends consideration of a liquid biopsy based comprehensive genomic profiling assay in patients who have metastatic or advanced gastric cancer who may be unable to safely undergo a traditional biopsy (p. GAST-B, 6 of 7).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Histiocytic Neoplasms 1.2025
https://www.nccn.org/professionals/physician_gls/pdf/histiocytic_neoplasms.pdf

This guideline mentions molecular testing in the workup for histiocytosis and states that if biopsy is not possible due to location or risk factors, mutational analysis of peripheral blood is an option (p. LCH-1A, ECD-1A).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma 2.2025
https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf

This guideline recommends tumor molecular profiling for patients with locally advanced, metastatic disease, recurrence after resection, or disease progression if anti-cancer treatment is being considered. While testing of tumor tissue is preferred, cell-free DNA testing can be

considered if tumor tissue testing is not feasible (p. PANC-1, PANC-1A, PANC-5, PANC-6A, PANC-9, PANC-10, PANC-11).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ampullary Adenocarcinoma 2.2025
https://www.nccn.org/professionals/physician_gls/pdf/ampullary.pdf

This guideline recommends somatic molecular profiling for patients with locally advanced or metastatic disease when systemic therapy is being considered. Testing on tumor tissue is preferred but cell-free DNA testing can be considered if tumor tissue testing is not feasible (p. MS-5, AMP-3, AMP-6, AMP-7).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Occult Primary 2.2025
https://www.nccn.org/professionals/physician_gls/pdf/occult.pdf

This guideline recommends consideration of molecular profiling of tumor tissue after an initial determination of histology has been made. Testing on tumor tissue is preferred; however, cell-free DNA testing can be considered if tumor tissue testing is not feasible (p. OCC-1A, OCC-2).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer 2.2026
https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

This guideline recommends evaluating prostate tumors for mutations in homologous recombination DNA repair genes (such as BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2, and CDK12) in individuals with metastatic prostate cancer. In addition, MSI evaluation is recommended for metastatic prostate cancer. Plasma circulating tumor (ctDNA) assay is an option if biopsy is not feasible, but should be collected when there is radiographic or biochemical progression (ie elevated PSA) to reduce the risk of false negatives. In patients with undetectable PSA levels, the NCCN recommends against ctDNA collection (PROS-C, 2 of 2).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Esophageal and Esophagogastric Junction Cancers 4.2025
https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf

This guideline recommends consideration of a liquid biopsy based comprehensive genomic profiling assay in patients who have metastatic or advanced cancer who may be unable to safely undergo a traditional biopsy or when insufficient tumor tissue is available (p. ESOPH-B, 6 of 7).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Colon Cancer 4.2025
https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf

This guideline recommends broad molecular profiling for detection of mutations in RAS, BRAF and other genes along with HER2 amplifications and MSI during the initial workup or at recurrence in patients with suspected or proven metastatic adenocarcinoma (COL-2, COL-9). Testing may be done via blood- or tissue-based NGS panels (COL-B 4 of 10). NCCN recommends consideration of repeat testing after targeted therapy to guide future treatment decisions (p. COL-B, 4 of 10). The NCCN does not recommend molecular profiling via ctDNA for surveillance or de-escalation of care (COL-8, COL-4).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer 8.2025
https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

This guideline recommends broad-based molecular profiling using ctDNA only when disease is advanced or metastatic adenocarcinoma, large cell, or NSCLC not otherwise specified (NOS). NCCN also recommends consideration of broad molecular profiling for advanced or metastatic squamous cell carcinoma (p. NSCL-19). Per NCCN, “[c]omplete genotyping for EGFR, KRAS, ALK, ROS1, BRAF, NTRK1/2/3, MET, RET, and ERBB2 (HER2) via biopsy and/or plasma testing” are recommended either on tissue, plasma, or both (p. NSCL-20). Both tissue and ctDNA testing have false negative rates and NCCN recommends consideration of complementary testing to increase the likelihood of mutation detection and reduce time to results (p. NSCL-19, NSCL-H, 8 of 8).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Melanoma: Cutaneous 2.2025
https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf

This guideline supports the use of cell-free circulating tumor DNA (ctDNA) if tumor tissue is unavailable (p. ME-C 3 of 8). In individuals with initial presentation in stage IV disease, broad genomic profiling using larger NGS panels is recommended if feasible, "especially if the test results might guide future treatment decisions or eligibility for participation in a clinical trial" (ME-C 4 of 8). If BRAF single-gene testing was already done and was negative, NCCN recommends consideration of a larger profiling panel to identify other potential biomarkers (p. ME-C 4 of 8). NCCN recommends tissue testing if testing via ctDNA is negative due to the risk of false negatives (ME-C 3 of 8).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Cervical Cancer 1.2026
https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf

This guideline recommends consideration of comprehensive molecular profiling for cervical cancer that is persistent or recurrent after treatment. If biopsy of the metastatic site is not feasible or if no tissue is available, testing can be done on circulating tumor DNA (p. CERV-10).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Biliary Tract Cancers 2.2025
https://www.nccn.org/professionals/physician_gls/pdf/btc.pdf

This guideline recommends comprehensive molecular profiling for patients with unresectable or metastatic biliary tract cancer who are candidates for when systemic therapy is an option. NCCN recommends consideration of a cell-free DNA test if there is not enough tissue available or repeat biopsy cannot be done (p. BIL-B, 1 of 8).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Neuroendocrine and Adrenal Tumors. Version 3.2025.
https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf

This guideline recommends consideration of tumor molecular profiling for patients with locoregional unresectable/metastatic extrapulmonary poorly differentiated neuroendocrine carcinoma/large or small cell carcinoma/mixed neuroendocrine-non-neuroendocrine neoplasm, pheochromocytoma/paraganglioma, and atypical carcinoid neoplasms when systemic therapy is being considered (NET-6, NET-11, NET-12, WDG3-1, PHEO-1). Testing on tumor tissue is preferred, however, cell-free DNA testing can be considered if tumor tissue testing is not feasible (p. PDNEC-1, PDNEC-1A).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer 3.2025
https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf

This guideline recommends somatic testing for BRCA1/2 and homologous recombination deficiency status for patients at diagnosis and broader molecular testing in the recurrence setting, especially for less common histologies with limited approved treatment options. Testing may be performed on circulating tumor DNA (ctDNA or liquid biopsy) when tissue-based analysis is not clinically feasible (p. OV-B, 1 of 3).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer 5.2025
https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

This guideline recommends the use of comprehensive somatic profiling for patients with stage IV or recurrent invasive breast cancer to identify candidates for additional targeted therapies (BINV-18, BINV-Q 6 of 15). Biomarker testing should be done on at least the first recurrence, and either tissue or plasma based assays can be used, and testing of an alternate specimen can be considered if one is negative for actionable biomarkers (p. BINV-18).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Small Cell Lung Cancer 2.2026
https://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf

This guideline recommends consideration of comprehensive molecular profiling for extensive stage and relapsed small cell lung cancer (p. SCL-B, 1 of 2), which is defined as stage IV cancer and stage III cancer with extensive local lung nodules or nodal volume (ST-1). Testing may be performed on blood, tissue, or both (p.SCL-B, 1 of 2).

Definitions

1. **Advanced** cancer (advanced stages or advanced tumor or advanced/metastatic): Cancer that is unlikely to be cured or controlled with treatment. The cancer may have spread from where it first started to nearby tissue, lymph nodes, or distant parts of the body. Treatment may be given to help shrink the tumor, slow the growth of cancer cells, or relieve symptoms.
2. **Advanced** cancer (advanced stages or advanced tumor or advanced/metastatic) is unlikely to be cured or controlled with treatment. The cancer may have spread from where it first started to nearby tissue, lymph nodes, or distant parts of the body. Treatment may be given to help shrink the tumor, slow the growth of cancer cells, or relieve symptoms.
3. **Breast cancer** is a term that applies to patients with invasive cancer or ductal carcinoma in situ (DCIS).
4. **Circulating tumor DNA (ctDNA)** is fragmented, tumor-derived DNA circulating in the bloodstream that is not being carried in a cell. ctDNA derives either directly from the tumor or from circulating tumor cells.

Broad Molecular Profiling Panels for Hematologic Malignancies and Myeloid Malignancy Panels

I. Broad molecular profiling panels for hematologic malignancies and myeloid malignancy panels in bone marrow or peripheral blood are considered **medically necessary** when:

A. The member is undergoing evaluation for acute myeloid leukemia (AML), **OR**

B. The member has newly diagnosed acute lymphoblastic leukemia (ALL), **OR**

C. The member has a newly diagnosed myelodysplastic syndrome (MDS), **OR**

D. The member has a suspected myelodysplastic syndrome (MDS), **AND**

1. Other causes of cytopenia(s) have been ruled out, **OR**

E. The member is suspected to have a myeloproliferative neoplasm (MPN), **AND**

1. This is the member's initial genetic evaluation for suspected MPN, **OR**

2. Previous results of *JAK2*, *CALR*, and *MPL* analysis were negative, **OR**

F. The member has a diagnosis of chronic myelogenous leukemia (CML), **AND**

1. There has been progression to accelerated or blast phase, **OR**

2. Results of *BCR-ABL1* kinase domain mutation analysis were negative, **OR**

G. The member has a diagnosis of diffuse large B-cell lymphoma, **OR**

H. The member is being evaluated for Langerhans Cell Histiocytosis (LCH), **OR**

I. The member is being evaluated for Erdheim-Chester Disease (ECD), **OR**

J. The member is being evaluated for Rosai-Dorfman Disease (RDD), **OR**

K. The member has a cutaneous T-cell lymphoma (CTCL).

II. Repeat broad molecular profiling panels for hematologic malignancies and myeloid malignancy panels in bone marrow or peripheral blood are considered **medically necessary** when:

A. The member has a myelodysplastic syndrome (MDS), **AND**

1. The member has relapsed after allo-HCT (hematopoietic cell transplant), **OR**

B. The member has acute lymphoblastic leukemia (ALL), **AND**

1. The member is showing evidence of symptomatic relapse after maintenance therapy, **OR**

C. The member has acute myeloid leukemia (AML), **AND**

1. The member has relapsed or refractory disease after consolidation or progression on treatment.

III. Broad molecular profiling panels for hematologic malignancies and myeloid malignancy panels in bone marrow or peripheral blood are considered **investigational** for all other indications.

NOTE: If a multigene panel is performed, appropriate panel codes should be used. These clinical criteria are not intended to address liquid biopsies.

Rationale and References

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Acute Myeloid Leukemia 3.2026
https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf

This guideline recommends molecular testing via multiplex gene panels and targeted analysis by next-generation sequencing for adult patients for purposes of prognostication, therapy, ongoing management (p. EVAL-1, EVAL-2A), and in the presence of relapsed or refractory disease after completion of consolidation (p. AML-8, AML-J 1 of 4).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Myelodysplastic Syndromes 3.2026
https://www.nccn.org/professionals/physician_gls/pdf/mds.pdf

This guideline recommends molecular testing during the initial evaluation of suspected myelodysplasia in patients with cytopenia. Testing should be performed on bone marrow or peripheral blood for somatic mutations in genes associated with myelodysplastic syndromes (p. MDS-1, MDS-1A).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Myeloproliferative Neoplasms 2.2025
https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf

This guideline recommends molecular testing on blood or bone marrow for patients suspected of having a myeloproliferative neoplasm. This testing can be done in a stepwise manner, or as an NGS multigene panel that includes JAK2, CALR and MPL. Once a diagnosis is confirmed, additional testing for somatic mutations is recommended for prognostication (p. MPN-1).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Chronic Myeloid Leukemia 1.2026
https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf

This guideline recommends consideration of testing for myeloid mutations for patients with advanced phase chronic myeloid leukemia (CML) who are in either accelerated or blast phase (CML-1). NCCN recommends consideration of panel testing for myeloid mutations in patients on TKI therapy who have progressed to accelerated or blast phase if they lack a BCR-ABL1 kinase domain mutation (p. CML-E).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: B-Cell Lymphomas 1.2026
https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf

This guideline recommends consideration of an NGS panel (BCEL-1) during the diagnostic evaluation for diffuse large B-cell lymphoma, to include at a minimum more than 50 genes with known clinical association (BCEL-A 1 of 3).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Primary Cutaneous Lymphomas 1.2026
https://www.nccn.org/professionals/physician_gls/pdf/primary_cutaneous.pdf

This guideline recommends consideration of multigene panel testing (MGPT) in individuals being worked up for or diagnosed with subcutaneous panniculitis-like T-cell lymphoma (SPTCL), mycosis fungoides/Sezary syndrome, and primary cutaneous CD30+ T-cell lymphoproliferative disorders (p. SPTCL-1, MFSS-1). The guideline states that MGPT is being used more often and is a more sensitive test for disease prognostication and monitoring (p. PCLYM-B 1 of 2).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Acute Lymphoblastic Leukemia 2.2025
https://www.nccn.org/professionals/physician_gls/pdf/all.pdf

This guideline recommends that patients diagnosed with acute lymphoblastic leukemia should undergo molecular characterization of their disease, including comprehensive testing for gene fusions and pathogenic mutations (p. ALL-1). Additionally, patients who are undergoing

surveillance after maintenance therapy and are showing evidence of symptomatic relapse should undergo repeat testing (p. ALL-8).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Histiocytic Neoplasms 2.2025
https://www.nccn.org/professionals/physician_gls/pdf/histiocytic_neoplasms.pdf

This guideline recommends molecular mutation profiling in the workup/evaluation of Langerhans Cell Histiocytosis (LCH), Erdheim-Chester Disease (ECD) and Rosai-Dorfman Disease (RDD) for prognostic and treatment information (p. HIST-C, 1 of 5).

Definitions

N/A

Chromosomal Microarray Analysis (CMA) for Pregnancy Loss

1. Chromosomal microarray analysis on products of conception (POC) may be considered **medically necessary** as an alternative to conventional karyotype analysis when:

    1. The member meets one of the following:

        1. The member has a history of recurrent pregnancy loss, **OR**

        2. The member has a pregnancy loss at or greater than 20 weeks of gestation (i.e., IUFD or stillbirth), **AND**

    2. The member has received counseling regarding the benefits and limitations of chromosome microarray analysis on products of conception.

2. Chromosome microarray analysis on products of conception (POC) is considered **investigational** for all other indications.

Rationale and References

Papas RS, Kutteh WH. Genetic testing for aneuploidy in patients who have had multiple miscarriages: a review of current literature. Appl Clin Genet. 2021;14:321-329.

A review published in the Application of Clinical Genetics in 2021 by Papas and Kutteh recommends that genetic testing on products of conception should be performed after the second and subsequent pregnancy loss. Chromosome microarray is the preferred testing method (p. 321).

Practice Committee of the American Society for Reproductive Medicine. Evaluation and treatment of recurrent pregnancy loss: a committee opinion. Fertil Steril. 2012;98(5):1103-1111. doi:10.1016/j.fertnstert.2012.06.048

The American Society for Reproductive Medicine (2012) issued an opinion on the evaluation and treatment of recurrent pregnancy loss. The statement drew multiple conclusions, one of which states: “Evaluation of recurrent pregnancy loss can proceed after 2 consecutive clinical pregnancy losses" (p. 1108).

Committee on Genetics and the Society for Maternal-Fetal Medicine. Committee Opinion No.682: Microarrays and Next-Generation Sequencing Technology: The Use of Advanced Genetic Diagnostic Tools in Obstetrics and Gynecology. Obstet Gynecol. 2016;128(6):e262-e268. doi:10.1097/AOG.0000000000001817

The ACOG and SMFM practice bulletin no. 682 supports the following evaluation for pregnancy loss in their 2016 statement (reaffirmed 2020, 2023 and 2025): "Chromosomal microarray analysis of fetal tissue (i.e., amniotic fluid, placenta, or products of conception) is recommended in the evaluation of intrauterine fetal death or stillbirth when further cytogenetic analysis is desired because of the test’s increased likelihood of obtaining results and improved detection of causative abnormalities" (p. e263).

Definitions

1. **Recurrent pregnancy loss (RPL)** is defined as having two or more failed clinical pregnancies, including a current loss if applicable

Chromosomal Microarray Analysis (CMA) for Prenatal Diagnosis

1. Chromosome microarray analysis for prenatal diagnosis via amniocentesis, CVS, or PUBS may be considered **medically necessary** when:

    1. The member has received counseling regarding the benefits and limitations of prenatal screening and diagnostic testing (including chromosome microarray via amniocentesis, CVS or PUBS) for fetal chromosome abnormalities, **AND**

    2. The member is NOT simultaneously undergoing karyotype analysis.

2. Chromosome microarray analysis for prenatal diagnosis via amniocentesis, CVS, or PUBS is considered **investigational** for all other indications.

Rationale and References

American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Obstetrics; Committee on Genetics; Society for Maternal–Fetal Medicine. Practice Bulletin No. 162: Prenatal Diagnostic Testing for Genetic Disorders. Obstet Gynecol. 2016 (Reaffirmed 2020 and 2024);127(5):e108-e122. doi:10.1097/AOG.0000000000001405

ACOG practice bulletin no. 162 (2016, reaffirmed 2020 and 2024) states the following: Chromosomal microarray is recommended to be offered to “any patient choosing to undergo invasive diagnostic testing” (p. e117) Chromosome microarray is recommended “as the primary test (replacing conventional karyotype)” when fetal structural abnormalities are detected by ultrasound examination (p. e117) In fetuses with signs and suggestive features of a specific aneuploidy, “karyotype with or without FISH may be offered before chromosomal microarray” (p. e117).

Committee on Genetics and the Society for Maternal-Fetal Medicine. Committee Opinion No.682: Microarrays and Next-Generation Sequencing Technology: The Use of Advanced Genetic Diagnostic Tools in Obstetrics and Gynecology. Obstet Gynecol. 2016 (reaffirmed 2020, 2023, and 2025);128(6):e262-e268. doi:10.1097/AOG.0000000000001817

The joint ACOG-SMFM committee opinion no. 682 (2016, reaffirmed 2020, 2023, and 2025) recommends that prenatal chromosome microarray analysis (CMA) be performed for a fetus with one or more structural anomalies, and this test can replace the need for fetal karyotype (p. 1). They also state that in a structurally normal fetus, either fetal karyotyping or CMA can be performed if the patient is undergoing invasive prenatal diagnostic testing (p. 1-2).

American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Obstetrics; Committee on Genetics; Society for Maternal-Fetal Medicine. Screening for Fetal Chromosomal Abnormalities: ACOG Practice Bulletin, Number 226. Obstet Gynecol. 2020 (Reaffirmed 2024);136(4):859-867. doi:10.1097/AOG.0000000000004084

ACOG practice bulletin no. 226 (2020, reaffirmed 2024) states the following regarding counseling patients: “Each patient should be counseled in each pregnancy about options for testing for fetal chromosomal abnormalities. It is important that obstetric care professionals be prepared to discuss not only the risk of fetal chromosomal abnormalities but also the relative benefits and limitations of the available screening and diagnostic tests” (p. 859).

Definitions

1. **Amniocentesis** is a procedure in which a sample of amniotic fluid is removed from the uterus for prenatal diagnostic testing.

Chromosomal Microarray Analysis for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, or Congenital Anomalies

1. Chromosomal microarray analysis for developmental delay, intellectual disability, autism spectrum disorder, or congenital anomalies is considered **medically necessary** when:

    1. The member has global developmental delay and/or intellectual disability, **OR**

    2. The member has autism spectrum disorder, **OR**

    3. The member has multiple congenital anomalies not specific to a well-delineated genetic syndrome, **OR**

    4. The member has short stature.

2. Chromosomal microarray analysis for developmental delay, intellectual disability, autism spectrum disorder, or congenital anomalies is considered **investigational** for all other indications.

Rationale and References

Mintz CS, Seaver LH, Irons M, Grimberg A, Lozano R, ACMG Professional Practice and Guidelines Committee. Focused Revision: ACMG practice resource: Genetic evaluation of short stature. Genet Med. 2021;23(5):813-815.

A 2021 focused revision to the ACMG practice resource entitled “Genetic evaluation of short stature,” supports CMA testing in cases of idiopathic short stature, small for gestational age with persistent short stature, and syndromic short stature (p. 813).

Manning M, Hudgins L; Professional Practice and Guidelines Committee. Array-based technology and recommendations for utilization in medical genetics practice for detection of

chromosomal abnormalities. Genet Med. 2010;12(11):742-745. Reaffirmed 2020. doi:10.1097/GIM.0b013e3181f8baad

The ACMG (2010, reaffirmed 2020) published a clinical practice resource on array-based technologies and their clinical utilization for detecting chromosomal abnormalities. They recommend CMA testing for individuals with the following (p. 744): Multiple anomalies not specific to a well-delineated genetic syndrome Apparently nonsyndromic DD/ID ASD [autism spectrum disorder]

Hyman SL, Levy SE, Myers SM; COUNCIL ON CHILDREN WITH DISABILITIES, SECTION ON DEVELOPMENTAL AND BEHAVIORAL PEDIATRICS. Identification, Evaluation, and Management of Children With Autism Spectrum Disorder. Pediatrics. 2020;145(1):e20193447. Reaffirmed 2025. doi:10.1542/peds.2019-3447

In the AAP's guideline entitled, "Identification, Evaluation, and Management of Children With Autism Spectrum Disorder," they recommend CMA testing in individuals with Autism Spectrum Disorder when there are no other suspected genetic syndromes for which more target testing exists (p. 16).

Rodan LH, Stoler J, Chen E, Geleske T; Council on Genetics. Genetic Evaluation of the Child With Intellectual Disability or Global Developmental Delay: Clinical Report. Pediatrics. 2025;156(1):e2025072219. doi:10.1542/peds.2025-072219

In their 2025 guideline entitled "Genetic Evaluation of the Child With Intellectual Disability or Global Developmental Delay: Clinical Report," the AAP recommends CMA as a first-tier agnostic test for children with global developmental delay and intellectual disability.

In this guideline, they define global developmental delay as a child under the age of five who has not met expected milestones in several areas of functioning, aligning with the definition put forth by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5). Genetic testing for developmental delay in only one area of functioning is not discussed in this guideline.

Definitions

1. **Autism spectrum disorder** is defined in the DSM V as persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history:
   1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.
   2. Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.
   3. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.
2. **Congenital anomalies** (according to ACMG) are anomalies not specific to a well-delineated genetic syndrome. These are structural or functional abnormalities requiring medical intervention that are usually evident at birth, or shortly thereafter, and are consequential to an individual's life expectancy, health status, or physical/social functioning.
3. **Developmental delay** (DD) is defined as slow-to-meet or not reaching milestones in one or more of the areas of development (communication, motor, cognition, social-emotional, or adaptive skills) in the expected way for a child's age.
4. **Global Developmental delay** is diagnosed when a child under age 5 is slow-to-meet or not reaching milestones in the expected way for their age in at least two areas of development (communication, gross/fine motor, cognition, social-emotional, or adaptive skills). Examples include (but are not limited to): not sitting independently by 9 months; not crawling or rolling over by a year; not walking by 18 months (based on CDC Developmental milestones)**.**
5. **Intellectual disability (ID)** is defined by the DSM V as an individual age 5 or older with either an IQ score of 70 or below, OR with a clinical diagnosis of intellectual disability per the DSM V, which includes all of the following:

1. Deficits in intellectual functions, such as reasoning, problem solving, planning, abstract thinking, judgment, academic learning, and learning from experience, confirmed by both clinical assessment and individualized, standardized intelligence testing.
2. Deficits in adaptive functioning that result in failure to meet developmental and sociocultural standards for personal independence and social responsibility. Without ongoing support, the adaptive deficits limit functioning in one or more activities of daily life, such as communication, social participation, and independent living, across multiple environments, such as home, school, work, and community.
3. Onset of intellectual and adaptive deficits during the developmental period.

6. **Multiple congenital anomalies,** according to ACMG, are not specific to a well-delineated genetic syndrome. These anomalies are structural or functional abnormalities usually evident at birth, or shortly thereafter, and can be consequential to an individual's life expectancy, health status, physical or social functioning, and typically require medical intervention.

Colorectal Cancer Prognostic Algorithmic Tests

1. Colorectal cancer prognostic algorithmic tests are considered **investigational** for all indications.

Rationale and References

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Colon Cancer 4.2025
https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf

This guideline does not recommend multigene panel assays to assist in making clinical decisions about adjuvant therapy, citing insufficient evidence for their use (p. COL-4).

Definitions

N/A

Comprehensive Connective Tissue Disorders Multigene Panel

1. Comprehensive connective tissue disorders multigene panel analysis is considered **medically necessary** when:

    1. The member meets criteria for at least one of the following (see specific coverage criteria sections below):

        1. Marfan Syndrome

        2. Loeys-Dietz Syndrome

        3. Classic Ehlers-Danlos Syndrome

        4. Vascular Ehlers-Danlos Syndrome (vEDS).

2. Comprehensive connective tissue disorders multigene panel analysis is considered **investigational** for all other indications, including isolated hypermobility and hypermobile Ehlers-Danlos syndrome (hEDS).

NOTE: If a panel is performed, the appropriate panel code should be used

Rationale and References

Levy HP. Hypermobile Ehlers-Danlos Syndrome. 2004 Oct 22 [Updated 2024 Feb 22]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews[Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1279/

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online.

Per the Hypermobile Ehlers-Danlos Syndrome (EDS) GeneReviews, there are currently no genetic etiologies that have been identified for hypermobile EDS.

Dietz H. FBN1-Related Marfan Syndrome. 2001 Apr 18 [Updated 2022 Feb 17]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1335/

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online.

Per the FBN1-Related Marfan Syndrome GeneReviews, a Marfan syndrome, Loeys-Dietz Syndrome, and familial thoracic aortic aneurysms and dissections multigene panel is an appropriate testing approach.

Loeys BL, Dietz HC. Loeys-Dietz Syndrome. 2008 Feb 28 [Updated 2024 Sep 12]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1133/

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online.

Per the Loeys-Dietz Syndrome (LDS) GeneReviews, it may be appropriate to order a multigene panel for Marfan syndrome/LDS/familial thoracic aortic aneurysms and dissections for genes associated with disorders that can include aortic aneurysms and dissections.

Malfait F, Symoens S, Syx D. Classic Ehlers-Danlos Syndrome. 2007 May 29 [Updated 2024 Feb 1]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1244/

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online.

The GeneReviews for Classic Ehlers-Danlos Syndrome (EDS) states that multigene panels that include COL5A1 and COL5A2 and other genes relating to EDS is an appropriate testing strategy.

***Byers PH. Vascular Ehlers-Danlos Syndrome. 1999 Sep 2 [Updated 2025 Apr 10]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1494/ ***

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online.

Per the Vascular Ehlers-Danlos Syndrome GeneReviews, the use of a multigene panel which includes genes associated with similar genetic disorders, such as Marfan Syndrome and Loeys-Dietz syndrome, is appropriate.

Definitions

N/A

Cutaneous Melanoma Diagnostic Algorithmic Tests

1. Cutaneous melanoma diagnostic algorithmic tests are considered **medically necessary** when:

    1. The member has a melanocytic neoplasm that is diagnostically uncertain or equivocal after histopathology.

2. Cutaneous melanoma diagnostic algorithmic tests are considered **investigational** for all other indications, including:

    1. A melanocytic neoplasm that has pathology definitive for melanoma, desmoplastic melanoma, or sclerosing nevus.

Rationale and References

Swetter SM, Tsao H, Bichakjian CK, et al. Guidelines of care for the management of primary cutaneous melanoma. J Am Acad Dermatol. 2019;80(1):208-250. doi:10.1016/j.jaad.2018.08.055

In 2019, the American Academy of Dermatology published an article titled “Guidelines of care for the management of primary cutaneous melanoma”. The guidelines consider diagnostic testing for cutaneous melanoma to be “largely investigative” and do not recommend them for routine use; however, it may be an appropriate ancillary test for equivocal melanocytic neoplasms. This includes gene expression profiling (GEP) as a routine diagnostic test for individuals with cutaneous melanoma (p. 219).

AUC Committee Members, Fung MA, Vidal CI, et al. Appropriate use criteria for ancillary diagnostic testing in dermatopathology: New recommendations for 11 tests and 220 clinical scenarios from the American Society of Dermatopathology Appropriate Use Criteria Committee. J Cutan Pathol. 2022;49(3):231-245. doi:10.1111/cup.14135 Erratum in: J Cutan Pathol. 2024;51(7):555. doi:10.1111/cup.14594

The American Society of Dermatopathology (AUC Committee Members, 2022) published clinical scenarios where a 23 gene qRT-PCR test (MyPath Melanoma) was determined by a review of published evidence to be “majority usually appropriate.” The guideline also found that qRT-PCR testing for individuals with confirmed melanoma or nevus and adults with sclerosing (desmoplastic) nevus and desmoplastic melanoma were classified as “rarely inappropriate” clinical scenarios (p. 238 and Table 2, starting on p. 239).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Melanoma: Cutaneous 2.2025
https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf

This guideline recommends gene expression profiling (GEP) as an available test for diagnosing indeterminate melanocytic neoplasms by histopathology, along with several other ancillary tests (p. ME-C 1 of 8). NCCN recommends against the use of GEP testing during the initial workup of a stage 0 in situ, T1a, or T1b melanoma (p. ME-2 and ME-2A).

Definitions

N/A

Cutaneous Melanoma Prognostic Algorithmic Tests

1. Cutaneous melanoma prognostic algorithmic tests with insufficient evidence of clinical validity are considered **investigational** for all indications.

Rationale and References

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Melanoma: Cutaneous 2.2025
https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf

This guideline does not recommend the use of gene expression profiling (GEP) for patients with confirmed cutaneous melanoma, given the lack of prospective clinical utility data. The NCCN panel maintains that GEP should not replace standard clinical and pathological staging (p. ME-2A, ME-C 1 of 8).

Bartlett EK, O'Donoghue C, Boland G, et al. Society of Surgical Oncology Consensus Statement: Assessing the Evidence for and Utility of Gene Expression Profiling of Primary Cutaneous Melanoma. Ann Surg Oncol. 2025;32(3):1429-1442. doi:10.1245/s10434-024-16379-2

The SSO, in its 2024 consensus statement "Assessing the Evidence for and Utility of Gene Expression Profiling of Primary Cutaneous Melanoma," does not recommend the use of gene expression profiling (GEP) in adults with pT1a-pT4b primary cutaneous melanoma for predicting sentinel lymph node (SLN) status, guiding surveillance or follow-up approaches, or informing the use of adjuvant therapy due to insufficient high-level evidence (p. 2). These conclusions were reached through a rigorous process involving 20 experts, who used the PICOT framework to refine clinical questions and systematically reviewed 50 studies selected from over 130 articles. The recommendations were developed through the Modified Delphi process, achieving consensus with at least 80% agreement among a diverse panel of specialists (p. 4-6).

ECRI. DecisionDx-Melanoma (Castle Biosciences, Inc.) for Evaluating Prognosis and Guiding Management of Cutaneous Melanoma. Genetic Test Assessment. Published October 2023.

A review completed by ECRI (2023) found evidence for the DecisionDx-Melanoma 31-gene profiling (31-GEP) test to be somewhat favorable based on the available data pertaining to clinical validity, and potential clinical utility of the test. Specifically, the available studies demonstrated that they may improve patient outcomes (e.g., overall survival), by informing decisions to escalate surveillance when the test is added to best available care (i.e., tumor staging, SLNB). The review determined that current research does not provide sufficient evidence to conclude whether DecisionDx-Melanoma allows patients to safely skip sentinel lymph node biopsy (SLNB). Additional longitudinal studies are necessary to assess long-term health outcomes, such as recurrence, in patients who opt out of the biopsy.

Centers for Medicare & Medicaid Services. Medicare Coverage Database: Local Coverage Determination. MolDX: Melanoma Risk Stratification Molecular Testing (L38016). Revision effective May 15, 2025.
https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=38016&ver=19&

Cutaneous melanoma prognostic testing is addressed by the Local Coverage Determination (LCD), “MolDX: Melanoma Risk Stratification Molecular Testing” (L38016), which provides a path to coverage for the DecisionDx-Melanoma and Merlin test assays. However, these recommendations were established prior to the release of the Society of Surgical Oncology (SSO) guidelines, which represent the latest expert consensus in the field. Given the rapidly evolving landscape of precision medicine and the methodological rigor applied in developing these guidelines, we place greater weight on the SSO's recommendations as a more current and comprehensive standard for clinical practice.

Definitions

1. **Clinical validity,** according to the National Institutes of Health-Department of Energy (NIH-DOE) Task Force on Genetic Testing, describes the accuracy with which a test identifies a particular clinical condition. The components of measuring clinical validity are:

1. **Sensitivity**: among people with a specific condition, the proportion who have a positive test result

2. **Specificity**: among people who do not have the condition, the proportion who have a negative test result

3. **Positive predictive value**: among people with a positive test result, the proportion of people who have the condition

4. **Negative predictive value**: among people with a negative test result, the proportion who do not have the condition

Cutaneous Melanoma Risk Assessment Algorithmic Tests

1. Cutaneous melanoma risk assessment algorithmic tests are considered **medically necessary** when:

    1. The member has a melanocytic neoplasm that shows at least one ABCDE feature (**a**symmetry, **b**order irregularity, **c**olor variegation, **d**iameter >6 mm, and **e**volution), **AND**

    2. A biopsy is being considered but has not yet been performed, **AND**

    3. The use of the test is limited to a maximum of 2 times per visit.

2. Cutaneous melanoma risk assessment algorithmic tests are considered **investigational** for all other indications.

Rationale and References

Centers for Medicare & Medicaid Services. Medicare Coverage Database: Local Coverage Determination. MolDX: Pigmented Lesion Assay (L38051). Effective 02/10/2020. Updated 06/20/2024. https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=38151

Per MolDX: Pigmented Lesion Assay LCD (L38051), this test is used to determine whether a biopsy should be performed. The LCD lists characteristics for the skin lesion that are appropriate for testing, which includes having at least 1 ABCDE criteria.

The LCD also states that “Only 1 test may be used per patient per clinical encounter, in most cases. In roughly 10% of patients, a second test may be indicated for the same clinical encounter. For rare cases where more than 2 tests are indicated in a single clinical encounter, an appeal with supporting documentation may be submitted for additional tests.”

ECRI. Pigmented Lesion Assay (DermTech) for Aiding Melanoma Diagnosis. Genetic Test Assessment. Published March 2023.

A recent review completed by ECRI (2023) found evidence for the Pigmented Lesion Assay (PLA) to be somewhat favorable based on the available data demonstrating clinical validity and utility to improve patient outcomes when added to standard of care (p. 1).

Swetter SM, Tsao H, Bichakjian CK, et al. Guidelines of care for the management of primary cutaneous melanoma. J Am Acad Dermatol. 2019;80(1):208-250. doi:10.1016/j.jaad.2018.08.055

In their 2019 publication, the American Academy of Dermatology states that skin biopsy should be the initial step in establishing a diagnosis of cutaneous melanoma. The article mentions consideration of newer noninvasive techniques, including gene expression analysis (p. 211).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Melanoma: Cutaneous 2.2025
https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf

This guideline recommends consideration of “prediagnostic noninvasive patch testing” to help inform decisions regarding biopsy for patients with melanocytic neoplasms that are clinically/dermoscopically suspicious for melanoma (p. ME-12).

Swetter S, Geller A. Melanoma: Clinical features and diagnosis. In: UpToDate, Connor RF (Ed), Wolters Kluwer. Last update Oct 04, 2023.
https://www.uptodate.com/contents/melanoma-clinical-features-and-diagnosis

Per UpToDate, “patients with a pigmented lesion that is changing and has additional ABCDE (asymmetry, border irregularity, color variegation, diameter >6 mm, evolution) criteria” should be strongly considered for dermatology referral.

Definitions

1. **ABCDE feature** is an acronym for examining patients with a lesion that is suspicious for melanoma: **a**symmetry, **b**order irregularity, **c**olor variegation, **d**iameter >6 mm, and **e**volution.

Epilepsy Multigene Panel

1. The use of an epilepsy multigene panel is considered **medically necessary** when:

    1. The member has a history of unexplained epilepsy (i.e., seizures not caused by acquired etiology such as trauma, infection, structural brain abnormality, and/or stroke).

2. The use of an epilepsy multigene panel is considered **investigational** for all other indications.

Rationale and References

Smith L, Malinowski J, Ceulemans S, et al. Genetic testing and counseling for the unexplained epilepsies: An evidence-based practice guideline of the National Society of Genetic Counselors. J Genet Couns. 2023;32(2):266-280. doi:10.1002/jgc4.1646

The National Society of Genetic Counselors (NSGC) published evidence-based practice guidelines for individuals with unexplained epilepsy. The NSGC recommendations are as follows (page 4): Individuals with unexplained epilepsy should be offered genetic testing, without limitation of age. Multi-gene, comprehensive testing, such as exome sequencing, genome sequencing or a multigene panel as a first-tier test is strongly recommended*

Per the practice guideline, the multi-gene panel should have a minimum of 25 genes and include copy number analysis. However, specific genes to be included in such panels were not outlined in the guidelines. For this reason, the number of genes included in the multi-gene panel was not added to the clinical coverage criteria. In rare situations, an epilepsy panel of fewer than 25 genes may be performed, in which case alternate coverage criteria should be used (please refer to Concert medical policy “General Approach to Genetic and Molecular Testing”).

Definitions

N/A

Evidence-Based Donor-Derived Cell-free DNA for Solid Organ Transplant Rejection

I. The use of peripheral blood measurement of donor-derived cell-free DNA in the management of patients after solid organ transplantation is considered **medically necessary** when:

A. Peripheral blood measurement of donor-derived cell-free DNA has not been performed in the past twelve months, **AND**

B. The member meets one of the following:

1. The member has undergone heart transplantation, **AND**

a) The test is Allosure or Prospera, **OR**

2. The member has undergone kidney transplantation, **AND**

a) The test is Allosure, Prospera, Viracor TRAC Kidney dd-cfDNA, VitaGraft Kidney 2.0, VitaGraft Kidney Baseline, or VitaGraft Kidney Subsequent, **AND**

(1) The member meets at least one of the following:

(a) The member has clinical signs of acute rejection, **OR**

(b) A biopsy was done to check for signs of acute rejection and is inconclusive, **OR**

(c) The member is being monitored for adequate immunosuppression, **OR**

3. The member has undergone lung transplantation, **AND**

    a) The test is Allosure or Prospera, **AND**

        (1) The member meets at least one of the following:

            (a) The member has clinical signs of acute rejection, **OR**

            (b) A biopsy was done to check for signs of acute rejection and is inconclusive, **OR**

            (c) The member is being monitored for adequate immunosuppression.

II. The use of peripheral blood measurement of donor-derived cell-free DNA in the management of patients after solid organ transplantation is considered **investigational** for all other indications.

Rationale and References

Park S, Sellares J, Tinel C, Anglicheau D, Bestard O, Friedewald JJ. European Society of Organ Transplantation Consensus Statement on Testing for Non-Invasive Diagnosis of Kidney Allograft Rejection. Transpl Int. 2024;36:12115. Published 2024 Jan 4. doi:10.3389/ti.2023.12115

The European Society of Organ Transplantation (ESOT) published a Consensus Statement on Testing for Non-Invasive Diagnosis of Kidney Allograft Rejection, which states the following: “Recommendation 1.1: We suggest that clinicians consider measuring serial plasma dd-cfDNA in patients with stable graft function to exclude the presence of subclinical antibody mediated rejection” (p. 5). “Recommendation 2.1: We recommend that clinicians measure plasma dd-cfDNA in patients with acute graft dysfunction to exclude the presence of rejection, particularly antibody mediated rejection” (p. 6).

ASTS Statement on donor-derived cell-free DNA (dd-cf-DNA). Published online March 6, 2023, Updated October 2024. American Society of Transplant Surgeons. https://www.asts.org/docs/default-source/position-statements/asts-statement-on-donor-derived-cell-free-dna-(dd-cfdna)---updated-oct.-2024.pdf

In their position statement (2023, updated 2024), ASTS stated the following: "We recommend that dd-cfDNA [donor-derived cell-free DNA] may be utilized to rule out subclinical rejection for heart transplant recipients" (p. 5). In the same updated statement, ASTS included a section on the current state of evidence supporting a frequency schedule for dd-cfDNA testing in kidney transplant recipients. Overall, the ASTS recommends "serial dd-cfDNA" testing, but states that "the optimal surveillance testing frequency is unknown". In their summary of evidence, they state that additional research is needed to determine the optimal frequency for dd-cfDNA surveillance testing (p. 3-4).

Velleca A, Shullo MA, Dhital K, et al. The International Society for Heart and Lung Transplantation (ISHLT) guidelines for the care of heart transplant recipients. J Heart Lung Transplant. 2023;42(5):e1-e141. doi:10.1016/j.healun.2022.10.015

The 2023 ISHLT guidelines were reviewed to assess the recommended frequency for dd-cfDNA testing. Included in the guidelines is an example of a biopsy schedule (pp. E89-90, Table 13) for follow-up visits post-transplant. The 2023 updated guideline states that noninvasive gene expression profile testing (such as Allomap) may be included in these follow-up visits but notes that the schedule "serves merely as an example", and dd-cfDNA testing use or frequency is not addressed in the table. No clear evidence-based recommendations in ISHLT for the use of dd-cfDNA testing as a serial monitoring tool, or for a specific frequency of testing were identified.

Centers for Medicare & Medicaid Services. Medicare Coverage Database: Local Coverage Determination. MolDX: Molecular Testing for Solid Organ Allograft Rejection (L38582). Available at: https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=38582

The CMS local coverage determination (LCD) entitled "MolDX: Molecular Testing for Solid Organ Allograft Rejection" provides limited coverage for molecular testing to evaluate for active

rejection in solid organ transplant recipients. The determination supports ordering of such tests when a transplant-center-affiliated physician is considering a diagnosis of active rejection (AR), particularly in patients with significant contraindications to invasive procedures. CMS states that the intended use of the test must be one of the following: “To assist in the evaluation of adequacy of immunosuppression, wherein a non-invasive or minimally invasive test can be used in lieu of a tissue biopsy in a patient for whom information from a tissue biopsy would be used to make a management decision regarding immunosuppression, OR As a rule-out test for AR in validated populations of patients with clinical suspicion of rejection with a non-invasive or minimally invasive test to make a clinical decision regarding obtaining a biopsy, OR For further evaluation of allograft status for the probability of allograft rejection after a physician-assessed pretest, OR To assess rejection status in patients that have received a biopsy, but the biopsy results are inconclusive or limited by insufficient material”.

Concert. Note regarding Evidence-Based Donor-Derived Cell-free DNA for Solid Organ Transplant Rejection. Effective date 07/01/2026.

For assessing rejection in patients post-transplant, absent clear, specific and evidence-based guideline recommendations for a particular regimen of testing, a default frequency of once every 12 months will be adopted.

Definitions

N/A

Evidence-Based Lung Cancer Risk Assessment Algorithmic Tests

1. Lung cancer risk assessment algorithmic tests with sufficient evidence of clinical validity and utility are considered **medically necessary** when:

    1. The member is age 40 years or older, **AND**

    2. The member has a single lung nodule between 8 and 30 mm in diameter, **AND**

    3. The member has a risk of cancer of 50% or less according to the Mayo risk prediction algorithm, **AND**

    4. The member does NOT have a diagnosis of cancer (except for nonmelanoma skin cancer) within 5 years of the lung nodule detection.

2. Lung cancer risk assessment algorithmic tests with sufficient evidence of clinical validity and utility are considered **investigational** for all other indications where clinical validity and utility have not been demonstrated.

Rationale and References

Centers for Medicare & Medicaid Services. Medicare Coverage Database: Local Coverage Local Coverage Determination. MolDX: BDX-XL2 (L37031). Effective Date 04/28/2022. Available at: https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=37031

The CMS local coverage determination (LCD) entitled BDX-XL2 (L37031) includes the following coverage criteria for the NodifyXL2 test for the management of a lung nodule: Nodule must be between 8 and 30mm in diameter Patients must be 40 years or older Patients must have a pre-test cancer risk (as assessed by the Mayo Clinic Model for Solitary Pulmonary Nodules) of 50% or less. “The intended use of the test is to assist physicians in the management of lung nodules by identifying those lung nodules with a high probability of being benign. These lung nodules would then be candidates for non-invasive computed tomography (CT) surveillance instead of invasive procedures.”

Pritchett MA, Sigal B, Bowling MR, Kurman JS, Pitcher T, Springmeyer SC; ORACLE Study Investigators. Assessing a biomarker's ability to reduce invasive procedures in patients with benign lung nodules: Results from the ORACLE study. PLoS One. 2023 Jul 11;18(7):e0287409. PMID: 37432960; PMCID: PMC10335667 doi:10.1371/journal.pone.0287409.

A 2023 study titled: “Assessing a biomarker's ability to reduce invasive procedures in patients with benign lung nodules: Results from the ORACLE study” aimed to assess the clinical impact of proteomic integrated classifier (IC) tests (specifically, NodifyXL2), following confirmation of clinical validity (PANOPTIC trial) in 2018. The study included a matched cohort and ultimately found that “[p]atients with a benign nodule in the IC group underwent fewer invasive procedures (n = 8, 5%) compared to patients in the untested control group (n = 30, 19%), yielding…[a] relative reduction of 74%” (p. 6).

Kheir F, Uribe JP, Cedeno J, et al. Impact of an integrated classifier using biomarkers, clinical and imaging factors on clinical decisions making for lung nodules. J Thorac Dis. 2023;15(7):3557-3567. doi:10.21037/jtd-23-42

A 2023 retrospective study titled: “Impact of an integrated classifier using biomarkers, clinical and imaging factors on clinical decisions making for lung nodules” compared individuals with lung nodules who were evaluated with the integrated classifier (IC) test (NodifyXL2) versus individuals receiving standard of care. The findings showed that invasive procedures were decreased by 57.5% in individuals with indeterminate lung nodules “without missing a malignant diagnosis at 1-year follow-up)”, when compared to the control arm (p. 3563).

Definitions

1. **Clinical validity,** according to the National Institutes of Health-Department of Energy (NIH-DOE) Task Force on Genetic Testing, describes the accuracy with which a test identifies a particular clinical condition. The components of measuring clinical validity are:

    1. **Sensitivity**: among people with a specific condition, the proportion who have a positive test result

2. **Specificity**: among people who do not have the condition, the proportion who have a negative test result

3. **Positive predictive value**: among people with a positive test result, the proportion of people who have the condition

4. **Negative predictive value**: among people with a negative test result, the proportion who do not have the condition

Evidence-Based Lung Cancer Treatment Algorithmic Tests

1. Lung cancer treatment algorithmic tests with sufficient evidence of clinical validity and utility are considered **medically necessary** when:

    1. The member has a non-squamous non-small cell lung cancer (NSCLC), **AND**

    2. The member's tumor size is less than 5 cm, **AND**

    3. The member has no positive lymph nodes (stages I and IIa), **AND**

    4. The member is considering adjuvant platinum-containing chemotherapy.

2. Lung cancer treatment algorithmic tests with sufficient evidence of clinical validity and utility are considered **investigational** for all other indications where clinical validity and utility have not been demonstrated.

Rationale and References

Centers for Medicare & Medicaid Services. Medicare Coverage Database: Local Coverage Determination. MolDX: Predictive Classifiers for Early Stage Non-Small Cell Lung Cancer (L38238). Effective 06/14/2020. Updated 07/03/2025. Available at: https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=38238

The CMS local coverage determination (LCD) entitled "MolDX: Predictive Classifiers for Early Stage Non-Small Cell Lung Cancer" includes coverage criteria for tests for non-small cell lung cancer (NSCLC). It states that coverage is considered appropriate for individuals with non-squamous NSCLC whose tumor is less than 5 cm, and in whom lymph nodes are negative. The patient's provider must also be considering adjuvant platinum-containing chemotherapy.

Definitions

1. **Adjuvant** therapy is medication (such as chemotherapy or endocrine therapy) given after the surgical removal of a cancerous tumor.

2. **Clinical validity,** according to the National Institutes of Health-Department of Energy (NIH-DOE) Task Force on Genetic Testing, describes the accuracy with which a test identifies a particular clinical condition. The components of measuring clinical validity are:

    1. **Sensitivity**: among people with a specific condition, the proportion who have a positive test result

    2. **Specificity**: among people who do not have the condition, the proportion who have a negative test result

    3. **Positive predictive value**: among people with a positive test result, the proportion of people who have the condition

    4. **Negative predictive value**: among people with a negative test result, the proportion who do not have the condition

Evidence-Based Minimal Residual Disease (MRD) Testing by ctDNA for Bladder Cancer

1. Evidence-based minimal residual disease (MRD) tests performed via circulating tumor DNA (ctDNA) with sufficient evidence of clinical validity and utility in bladder cancer for monitoring of treatment response are considered **medically necessary** when:

    1. The member has a diagnosis of muscle-invasive bladder cancer (MIBC), **AND**

    2. The member's tumor has all of the following characteristics:

        1. Locally invasive (T2-4a), **AND**

        2. Node negative (N0), **AND**

        3. No metastasis (M0), **AND**

    3. All of the following:

        1. The member has undergone cystectomy within the last 12 months, **AND**

        2. The member has no radiographic evidence of disease, **AND**

        3. The member is currently receiving or being considered for adjuvant chemotherapy.

2. Evidence-based minimal residual disease (MRD) tests performed via circulating tumor DNA (ctDNA) with insufficient evidence of clinical validity and utility in bladder cancer for monitoring of treatment response and/or recurrence are considered **investigational** for all other indications.

Rationale and References

Powles T, Kann AG, Castellano D, et al. ctDNA-Guided Adjuvant Atezolizumab in Muscle-Invasive Bladder Cancer. N Engl J Med. Published online October 20, 2025. doi:10.1056/NEJMoa2511885

The IMvigor011 phase 3, double-blind, randomized trial by Powles et al. investigated the use of circulating tumor DNA (ctDNA) to guide adjuvant therapy with atezolizumab in patients with muscle-invasive bladder cancer (MIBC). Patients were initially enrolled into the surveillance phase of the IMvigor011 trial based on the following surveillance inclusion criteria:

- Age: Must be at least 18 years of age.
- Disease: Muscle-invasive bladder cancer (MIBC).
- Surgical Staging: (y)pT2-4aN0MO or (y)pT0-4aN+MO surgical staging.
- Disease Status: Disease-free as assessed radiographically by the investigator.
- Timing of Enrollment: Enrolled 6 to 24 weeks after cystectomy.
- Neoadjuvant Chemotherapy: Eligible regardless of whether they had received neoadjuvant chemotherapy previously.
- Adjuvant Chemotherapy (If no neoadjuvant chemo): For patients who had not received neoadjuvant chemotherapy, adjuvant chemotherapy must have been considered inappropriate due to patient ineligibility, the patient's decision to decline treatment, or the physician's decision (p. 2)

Patients who met the initial surveillance criteria and subsequently underwent randomization into the treatment phase (atezolizumab or placebo) had to meet the following additional criteria:

- Tested ctDNA-positive at any time during the surveillance period.
- Remained disease-free as assessed radiographically by the investigator (confirmed at an independent review facility).
- Met the general eligibility criteria for the treatment phase (p. 3)

The IMvigor011 trial demonstrated that ctDNA-guided adjuvant atezolizumab significantly improved survival outcomes for patients with muscle-invasive bladder cancer (MIBC) who had evidence of molecular residual disease (ctDNA-positive status) after cystectomy (p.9).

Specifically, individuals who received ctDNA-guided adjuvant atezolizumab had a longer disease-free survival (DFS) compared with placebo (9.9 months with atezolizumab versus 4.8 months with placebo). The median overall survival was also higher with atezolizumab (32.8 months) as compared with placebo (21.1 months). Additionally, among the 357 patients with persistent ctDNA-negative status, DFS was 95% at 1 year and 88% at 2 years.

There is **SUFFICIENT EVIDENCE** in the literature to recommend coverage of ctDNA tumor testing for treatment response in patients with muscle-invasive bladder cancer. The findings above support the clinical usefulness of ctDNA-based testing to guide adjuvant treatment decisions for bladder cancer.

We reviewed publicly available sources for indications that other MRD tests on the market have been validated clinically by a reputable independent third party for bladder cancer treatment monitoring indications and did not identify any. As such, we cannot verify the clinical validity of these tests and they are not covered for this indication.

Concert. Evidence Review for Coverage Determination: Circulating Tumor DNA (ctDNA) for Treatment and/or Recurrence Monitoring. Published 02/13/2026.

The IMvigor011 phase 3, double-blind, randomized trial by Powles et al. investigated the use of circulating tumor DNA (ctDNA) to guide adjuvant therapy with atezolizumab in patients with muscle-invasive bladder cancer (MIBC). Patients were initially enrolled into the surveillance phase of the IMvigor011 trial based on the following surveillance inclusion criteria:

- Age: Must be at least 18 years of age.
- Disease: Muscle-invasive bladder cancer (MIBC).
- Surgical Staging: (y)pT2-4aN0MO or (y)pT0-4aN+MO surgical staging.
- Disease Status: Disease-free as assessed radiographically by the investigator.

- Timing of Enrollment: Enrolled 6 to 24 weeks after cystectomy.
- Neoadjuvant Chemotherapy: Eligible regardless of whether they had received neoadjuvant chemotherapy previously.
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We reviewed publicly available sources for indications that other MRD tests on the market have been validated clinically by a reputable independent third party for bladder cancer treatment monitoring indications and did not identify any. As such, we cannot verify the clinical validity of these tests and they are not covered for this indication.

Definitions

1. **Adjuvant** therapy is medication (such as chemotherapy or endocrine therapy) given after the surgical removal of a cancerous tumor.

2. **Circulating tumor DNA (ctDNA)** is fragmented, tumor-derived DNA circulating in the bloodstream that is not being carried in a cell. ctDNA derives either directly from the tumor or from circulating tumor cells.

3. **Clinical validity,** according to the National Institutes of Health-Department of Energy (NIH-DOE) Task Force on Genetic Testing, describes the accuracy with which a test identifies a particular clinical condition. The components of measuring clinical validity are:

    1. **Sensitivity**: among people with a specific condition, the proportion who have a positive test result

    2. **Specificity**: among people who do not have the condition, the proportion who have a negative test result

    3. **Positive predictive value**: among people with a positive test result, the proportion of people who have the condition

    4. **Negative predictive value**: among people with a negative test result, the proportion who do not have the condition

Evidence-Based Minimal Residual Disease (MRD) Testing by ctDNA for Colorectal Cancer

1. Evidence-based minimal residual disease (MRD) tests performed via circulating tumor DNA (ctDNA) with sufficient evidence of clinical validity and utility in colorectal cancer for monitoring of treatment response are considered **medically necessary** when:

    1. The member has a diagnosis of colorectal cancer, **AND**

        1. The member's tumor has all of the following characteristics:

            1) Stage II (T3-T4), **AND**

            2) Node negative (N0), **AND**

            3) No metastasis (M0), **AND**

        2. All of the following:

            1) The member has undergone surgery within the last month, **AND**

            2) The member is being considered for adjuvant chemotherapy, **AND**

            3) The member has no radiographic evidence of disease.

2. Evidence-based minimal residual disease (MRD) tests performed via circulating tumor DNA (ctDNA) with insufficient evidence of clinical validity and utility in colorectal cancer for monitoring of treatment response and/or recurrence are considered **investigational** for all other indications.

Rationale and References

Tie J, Wang Y, Lo SN, et al. Circulating tumor DNA analysis guiding adjuvant therapy in stage II colon cancer: 5-year outcomes of the randomized DYNAMIC trial. Nat Med. 2025;31(5):1509-1518. doi:10.1038/s41591-025-03579-w

The DYNAMIC I trial by Tie, et al demonstrated that ctDNA-guided adjuvant chemotherapy (ACT) reduced the proportion of patients receiving ACT compared to standard management.

Patients were initially enrolled into the treatment phase of the DYNAMIC I trial based on the following inclusion criteria (p. 1510 and 1512):

- Disease: Colon or rectal adenocarcinoma with negative resection margins.
    - Patients were required to have no evidence of macroscopic metastatic disease on CT of the chest, abdomen, and pelvis performed within 8 weeks of enrollment.
- Surgical Staging: Stage II (T3-4, N0, M0)
    - Of note, some patients also had high risk tumor features, such as poor tumor differentiation, lymphovascular invasion, deficient MMR status, etc
- Treatment: Patients had to be medically fit for adjuvant oxaliplatin- or fluoropyrimidine-based chemotherapy

The studies key findings, which span a 5 year period, showed that the ctDNA-guided approach was associated with a reduced proportion of patients receiving adjuvant chemotherapy (ACT) (15%) compared to the standard management group (28%) (p. 1509). At a median follow-up of 59.7 months, the 5-year recurrence-free survival (RFS) was similar between the ctDNA-guided (88%) and standard management (87%) groups, with a hazard ratio of 1.01 and a log-rank P-value of 0.927, indicating that there is no significant difference in the rate of recurrence between the two groups (p. 1509). The 5-year overall survival (OS) was also similar (93.8% versus 93.3%) (p. 1510).

A postoperative ctDNA molecular tumor burden higher than the median (0.38 tumor-derived mutant molecules per milliliter plasma, TDMM) was associated with worse 5-year RFS (58.9% versus 95.2% for lower burden) and inferior 5-year OS (71.8% versus 100%) (p.1512).

There is **SUFFICIENT EVIDENCE** in the literature to recommend coverage of ctDNA tumor testing for individuals with stage II T3-T4 colorectal cancer. The findings above support the clinical usefulness of ctDNA-based testing to guide adjuvant treatment decisions for this cancer in the clinical setting described by the Tie et al clinical trial.

Concert. Evidence Review for Coverage Determination: Circulating Tumor DNA (ctDNA) for Treatment and/or Recurrence Monitoring. Published 02/13/2026.

Concert Evidence Review for Coverage Determination (Published 02/13/2026)

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- Surgical Staging: Stage II (T3-4, N0, M0)
    - Of note, some patients also had high risk tumor features, such as poor tumor differentiation, lymphovascular invasion, deficient MMR status, etc
- Treatment: Patients had to be medically fit for adjuvant oxaliplatin- or fluoropyrimidine-based chemotherapy

The studies key findings, which span a 5 year period, showed that the ctDNA-guided approach was associated with a reduced proportion of patients receiving adjuvant chemotherapy (ACT) (15%) compared to the standard management group (28%) (p. 1509). At a median follow-up of 59.7 months, the 5-year recurrence-free survival (RFS) was similar between the ctDNA-guided (88%) and standard management (87%) groups, with a hazard ratio of 1.01 and a log-rank P-value of 0.927, indicating that there is no significant difference in the rate of recurrence between the two groups (p. 1509). The 5-year overall survival (OS) was also similar (93.8% versus 93.3%) (p. 1510).

A postoperative ctDNA molecular tumor burden higher than the median (0.38 tumor-derived mutant molecules per milliliter plasma, TDMM) was associated with worse 5-year RFS (58.9% versus 95.2% for lower burden) and inferior 5-year OS (71.8% versus 100%) (p.1512).

There is **SUFFICIENT EVIDENCE** in the literature to recommend coverage of ctDNA tumor testing for individuals with stage II T3-T4 colorectal cancer. The findings above support the clinical usefulness of ctDNA-based testing to guide adjuvant treatment decisions for this cancer in the clinical setting described by the Tie et al clinical trial.

Definitions

1. **Adjuvant** therapy is medication (such as chemotherapy or endocrine therapy) given after the surgical removal of a cancerous tumor.

2. **Circulating tumor DNA (ctDNA)** is fragmented, tumor-derived DNA circulating in the bloodstream that is not being carried in a cell. ctDNA derives either directly from the tumor or from circulating tumor cells.

3. **Clinical validity,** according to the National Institutes of Health-Department of Energy (NIH-DOE) Task Force on Genetic Testing, describes the accuracy with which a test identifies a particular clinical condition. The components of measuring clinical validity are:

1. **Sensitivity**: among people with a specific condition, the proportion who have a positive test result

2. **Specificity**: among people who do not have the condition, the proportion who have a negative test result

3. **Positive predictive value**: among people with a positive test result, the proportion of people who have the condition

4. **Negative predictive value**: among people with a negative test result, the proportion who do not have the condition

Evidence-Based Prostate Cancer Risk Assessment and Diagnostic Algorithmic Tests

I. Prostate cancer risk assessment and diagnostic algorithmic tests with sufficient evidence of clinical validity and utility are considered **medically necessary** when:

A. The member meets all of the following:

1. The member has not had a prostate biopsy, **AND**

2. The member has at least one of the following:

a) Prostate specific antigen (PSA) greater than 3 ng/ml, **OR**

b) A digital rectal exam (DRE) that is suspicious for cancer, **AND**

3. The test is one of the following:

a) Prostate Health Index (PHI), **OR**

b) SelectMDx, **OR**

c) 4Kscore, **OR**

d) ExoDx Prostate Test, **OR**

e) MyProstateScore 2.0 (MPS2), **OR**

f) IsoPSA, **OR**

g) Stockholm3, **OR**

B. The member meets all of the following:

1. The member has had a prostate biopsy, **AND**

2. The result is one of the following:

    a) Atypia, suspicious for cancer, **OR**

    b) High-grade prostatic intraepithelial neoplasia (PIN), **OR**

    c) Benign, **AND**

3. The test is one of the following:

    a) Prostate Health Index (PHI), **OR**

    b) 4Kscore, **OR**

    c) ExoDx Prostate Test, **OR**

    d) MyProstateScore 2.0 (MPS2), **OR**

    e) IsoPSA, **OR**

    f) ConfirmMDx, **OR**

    g) Prosegna PCA3 assay.

II. The use of prostate cancer risk assessment and diagnostic algorithmic tests with sufficient evidence of clinical validity and utility are considered **investigational** for all other indications where clinical validity and utility have not been demonstrated.

Rationale and References

Wei JT, Barocas D, Carlsson S, et al. Early Detection of Prostate Cancer: AUA/SUO Guideline Part I: Prostate Cancer Screening. J Urol. 2023;210(1):46-53.

doi:10.1097/JU.0000000000003491 Erratum in: Journal of Urology [Internet]. 2025 Jul 1;214(1):111. doi.org/10.1097/JU.0000000000004546

The AUA/SUO published guidelines on the early detection of prostate cancer (2023). They state that clinicians and patients may use adjunctive urine or serum markers to inform the shared decision making process regarding prostate biopsy (initial and/or repeat biopsy). It is imperative clinicians are familiar with biomarkers, understand what information or data each test provides, and consider whether additional information will impact management decisions before ordering a test (conditional recommendation, evidence level C) (p. 21-22, 24).

Of note, conditional recommendations are non-directive statements used when the evidence indicates that there is no apparent net benefit or harm, or when the balance between benefits and risks/burden is unclear. For evidence level C, the balance between benefits and risks is unclear but net benefit or net harm is comparable to other options.

Centers for Medicare & Medicaid Services. Medicare Coverage Database: Local Coverage Determination. MolDX: Molecular Biomarkers to Risk-Stratify Patients at Increased Risk for Prostate Cancer (L39042). Effective 07/03/2022. Updated 07/03/2025. https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdId=39042&ver=7

The CMS local coverage determination (LCD) titled “Molecular Biomarkers to Risk-Stratify Patients at Increased Risk for Prostate Cancer” states the following regarding the medically necessary use of biomarker tests for prostate cancer risk stratification:

- The patient must have either:
    - No previous prostate biopsy, OR
    - A previous biopsy that was negative or showed "non-malignant but abnormal" findings (such as ASAP—atypical small acinar proliferation, or HGPIN—high-grade prostatic intraepithelial neoplasia).
- There must be a continued clinical suspicion of cancer based on:

- Elevated or rising PSA (Prostate-Specific Antigen) levels, and/or
- An abnormal DRE (Digital Rectal Examination).

- Before ordering the molecular test, the patient must have undergone a repeat PSA and/or DRE testing as recommended by consensus guidelines.
- The test result must be intended to help the clinician and patient decide whether or not to proceed with a (repeat) biopsy.

Multiple tests are listed that "may be billed in the post-biopsy setting," including Progensa PCA3 assay, ConfirmMDx assay, and MyProstateScore 2.0.

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer Early Detection 1.2026
https://www.nccn.org/professionals/physician_gls/pdf/prostate_detection.pdf

This guideline recommends consideration of biomarkers that improve the specificity of screening in patients considering biopsy after abnormal PSA and/or DRE. Specifically, NCCN recommends further evaluation for individuals with PSA "greater than 3 ng/ml and/or a very suspicious DRE" (p. PROSD-2). Biomarker testing is mentioned as part of this additional evaluation, and NCCN specifies the following tests as options for risk stratification: Prostate Health Index (PHI), SelectMDx, 4Kscore, ExoDx Prostate Test, MyProstateScore (MPS), Stockholm3, and IsoPSA (p. PROSD-3 and PROSD-A).

On page PROSD-4, NCCN also recommends consideration of biomarker tests to improve specificity when considering a repeat biopsy for biopsy results showing the following: atypia, suspicious for cancer; high-grade prostatic intraepithelial neoplasia (PIN); benign. These tests include those listed above (except for SelectMDX and Stockholm3) and ConfirmMDX.

Wei JT, Barocas D, Carlsson S, et al. Early Detection of Prostate Cancer: AUA/SUO Guideline Part II: Considerations for a Prostate Biopsy. J Urol. 2023;210(1):54-63. doi:10.1097/JU.0000000000003492

Definitions

1. **Clinical validity,** according to the National Institutes of Health-Department of Energy (NIH-DOE) Task Force on Genetic Testing, describes the accuracy with which a test identifies a particular clinical condition. The components of measuring clinical validity are:

    a. **Sensitivity**: among people with a specific condition, the proportion who have a positive test result

    b. **Specificity**: among people who do not have the condition, the proportion who have a negative test result

    c. **Positive predictive value**: among people with a positive test result, the proportion of people who have the condition

    d. **Negative predictive value**: among people with a negative test result, the proportion who do not have the condition

Hereditary Breast and/or Ovarian Cancer Susceptibility Panels

A hereditary breast and/or ovarian cancer susceptibility panel includes genes that are associated with an inherited susceptibility to breast cancer, ovarian cancer, or both.

I. Genetic testing using a hereditary breast and/or ovarian cancer susceptibility panel is considered **medically necessary** when:

A. The panel includes, at a minimum, the following genes: *BRCA1*, *BRCA2*, **AND**

B. The member has one of the following:

1. The member has a personal history of breast cancer < age 65, **OR**

2. The member has a personal history of epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer), **OR**

3. The member has a personal history of breast cancer, **AND**

a) One of the following:

(1) Ashkenazi Jewish ancestry, **OR**

(2) Male (sex assigned at birth), **OR**

(3) Triple-negative breast cancer, **OR**

(4) Pancreatic or ampullary cancer, **OR**

(5) Metastatic prostate cancer, **OR**

(6) High- or very-high-risk group prostate cancer, **OR**

(7) Multiple primary breast cancers (diagnosed synchronously or metachronously), **OR**

(8) The member has a close relative with any one of the following:

(a) Breast cancer diagnosed < age 50, **OR**

(b) Male breast cancer, **OR**

(c) Ovarian cancer, **OR**

(d) Pancreatic cancer, **OR**

(e) Prostate cancer that is either metastatic, intermediate-risk or high- or very-high-risk group), **OR**

b) There are 3 or more total diagnoses of breast cancer and/or prostate cancer (any grade) on the same side of the family including the member with breast cancer, **OR**

4. The member has a personal history of lobular breast cancer, **AND**

a) A personal or family history of diffuse gastric cancer, **OR**

5. The member has a personal history of non-epithelial ovarian cancer (sex-cord tumors with annular tubules [SCTAT] or small cell carcinoma of the ovary hypercalcemic type [SCCOHT]), **OR**

6. The member has a personal history of serous tubal intraepithelial carcinoma (STIC), **OR**

7. The member is unaffected or the member does not have a personal history of breast cancer that meets the above criteria, **AND**

    a) The member has a first- or second-degree relative diagnosed with breast cancer at or before age 50 years, **OR**

    b) The member has a first- or second-degree relative meeting any of criteria I.B.2, I.B.3, or I.B.4, **OR**

    c) The member's probability of having a *BRCA1* or *BRCA2* pathogenic variant is greater than 2.5% based on prior probability models (e.g., Tyrer-Cuzick, BRCApro, CanRisk), **OR**

8. The member has a personal history of breast cancer, **AND**

    a) The member has recurrent unresectable or metastatic breast cancer and is being considered for systemic treatment using PARP inhibitors, **OR**

    b) The member has recurrent or metastatic breast cancer and is being considered for adjuvant treatment with olaparib therapy.

II. Genetic testing using a STAT hereditary breast cancer panel is considered **medically necessary** when:

    A. The member meets any of the above criteria, **AND**

    B. The member requires a rapid turn-around-time for decision making related to surgical interventions or treatment.

III. Genetic testing using a hereditary breast and/or ovarian cancer susceptibility panel is considered **investigational** for all other indications.

IV. *BRCA1/BRCA2* mRNA sequencing analysis in genes associated with breast and/or ovarian cancers for the interpretation of variants of unknown significance is considered **investigational** because it is typically either considered an existing component of the genetic testing process for quality assurance or follow up testing without proven utility.

Rationale and References

Bedrosian I, Somerfield MR, Achatz MI, et al. Germline testing in patients with breast cancer: ASCO-Society of Surgical Oncology Guideline. J Clin Oncol. 2024;42(5):584-604. doi:10.1200/JCO.23.02225

Guidelines published by ASCO/SSO (2024) recommend BRCA1/2 testing to all newly diagnosed patients who are 65 years of age or younger at diagnosis (Type: Formal Consensus; Agreement 87.50%) (p. 590).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer 5.2025
https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

This guideline recommends germline *BRCA1, BRCA2,* and *PALB2* sequencing to determine eligibility for the FDA approved therapies olaparib and talazoparib in patients with “recurrent unresectable (local or regional) or stage IV (M1) disease” (p. BINV-Q 7 of 15).

The guideline also recommends germline *BRCA1* and *BRCA2* testing in patients with recurrent or metastatic breast cancer, regardless of HER2 status, to assess for PARPi eligibility (p. BINV-Q 2, 3, and 4 of 15).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate 2.2026 https://www.nccn.org/professionals/physician_gls/pdf/genetics_bopp.pdf

This guideline outlines clinical criteria for germline genetic testing of high-penetrance breast cancer genes. Criteria include:

1) Personal history of breast cancer at 50 years of age or younger (p. CRIT-2).

2) Personal history of breast cancer at any age with specific features (p. CRIT-2):

- Male breast cancer
- Ashkenazi Jewish ancestry
- Treatment indications
    - To aid in systemic treatment decisions using PARP inhibitors for metastatic breast cancer
- To aid in adjuvant treatment decisions with olaparib for high-risk, HER2-negative breast cancer
- Pathology/histology
    - Triple-negative breast cancer
    - Multiple primary breast cancers (synchronous or metachronous)
    - Lobular breast cancer if there is also a personal/family history of diffuse gastric cancer
- Family history of at least 1 close blood relative with:
    - Breast cancer at age 50 years or younger
    - Male breast cancer
    - Ovarian cancer
    - Pancreatic cancer
    - Prostate cancer with metastatic, or high- or very-high-risk group
    - 3 or more total diagnoses of breast cancer and/or prostate cancer in patient and/or close blood relatives on the same side of the family

3) Family history-based criteria (p. CRIT-2): Testing is also recommended in select unaffected individuals and those with a personal history that does not meet the above criteria. Qualifying scenarios include the presence of a first- or second-degree blood relative meeting any of the criteria listed above with the exception of relatives who meet criteria only for systemic therapy selection. If the affected relative has pancreatic cancer or prostate cancer, then only first-degree relatives should be offered testing unless indicated based on additional family history.

4) An affected or unaffected individual who otherwise does not meet the criteria above but has a probability of greater than 5% of a *BRCA1/2* pathogenic variant based on prior probability models (e.g., Tyrer-Cuzick, BRCAPro, CanRisk) (p. CRIT-2).

These guidelines also recommend consideration of testing for patients with a personal history of breast cancer diagnosed at or before age 65, patients diagnosed with breast cancer at any age with >1 close blood relative with intermediate-risk prostate cancer with intraductal/cribriform histology, and for patients affected or unaffected with breast cancer who otherwise do not meet any of the above criteria but with a 2.5%–5% probability of BRCA1/2 P/LP variant based on prior probability models (e.g., Tyrer-Cuzick, BRCAPro, CanRisk) (p. CRIT-3).

These guidelines also recommend that patients with epithelial ovarian cancer (including fallopian tube or peritoneal cancer) as well as patients with non-epithelial ovarian cancer (sex-cord tumors with annular tubules and small cell carcinoma of the ovary [hypercalcemic type]) at any age be offered germline genetic testing for multiple genes, including *ATM*, *BRCA1, BRCA2, BRIP1, MLH1, MSH2, MSH6, EPCAM, PALB2, RAD51C,* and *RAD51D* (p. CRIT-4). Additionally, NCCN recommends consideration of testing for these genes in individuals with a personal history of serous tubal intraepithelial carcinoma (STIC) at any age (p. CRIT-4).

Definitions

1. **Adjuvant** therapy is medication (such as chemotherapy or endocrine therapy) given after the surgical removal of a cancerous tumor.

2. **Adjuvant treatment with olaparib therapy** may be indicated for cancer defined as the following:

    a. Triple-negative breast cancer treated with either:

        i. Adjuvant chemotherapy with axillary node-positive disease or an invasive primary tumor greater than or equal to 2 cm on pathology analysis, **OR**

ii. Neoadjuvant chemotherapy with residual invasive breast cancer in the breast or resected lymph nodes, **OR**

b. Hormone receptor positive disease treated with either:

i. Adjuvant chemotherapy with four or more positive pathologically confirmed lymph nodes, **OR**

ii. Neoadjuvant chemotherapy which did not have a complete pathologic response, with a CPS+CG score [pre-treatment clinical (CS) and post-treatment pathological stage (PS), estrogen-receptor status (E) and grade (G)] of 3 or higher.

3. **Breast cancer** is a term that applies to patients with invasive cancer or ductal carcinoma in situ (DCIS).

Hereditary Dystonia Multigene Panel

1. Multigene panel analysis to establish a genetic diagnosis of hereditary dystonia is considered **medically necessary** when:

    1. The member has a clinical presentation consistent with dystonia or patterns of abnormal, repetitive, dystonic movements.

2. Multigene panel analysis to establish a genetic diagnosis of hereditary dystonia is considered **investigational** for all other indications.

Rationale and References

Koptielow J, Szyłak E, Szewczyk-Roszczenko O, et al. Genetic Update and Treatment for Dystonia. Int J Mol Sci. 2024;25(7):3571. Published 2024 Mar 22. doi:10.3390/ijms25073571

In their 2024 publication reviewing the genetic causes and treatments for dystonia, Koptielow et al. define dystonias as disorders of excessive muscle contractions that lead to atypical movements or postures that are often repetitive (p.1). Dystonias are classified as inherited or acquired diseases and they are either the primary symptom or a co-existing feature of other complex conditions (p. 3 and 4).

Definitions

N/A

Hereditary Gastrointestinal/Colorectal Cancer Susceptibility Panels

1. Genetic testing using a hereditary gastrointestinal/colorectal cancer susceptibility panel is considered **medically necessary** when:

    1. The member meets at least one of the following:

        1. The member has a personal history of, or at least one blood relative with any of the following:

            1) At least 10 adenomatous polyps, **OR**

            2) At least 2 hamartomatous polyps, **OR**

            3) At least 5 serrated polyps/lesions proximal to the rectum, **OR**

        2. The member meets testing criteria for Lynch syndrome/HNPCC *MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM* Sequencing and/or Deletion/Duplication Analysis, **AND**

    2. The panel includes, at a minimum, sequencing of the following genes: *APC, MUTYH, MLH1, MSH2, MSH6, PMS2, EPCAM, BMPR1A, SMAD4, PTEN, STK11,* and *TP53*.

2. Genetic testing using a hereditary gastrointestinal/colorectal cancer susceptibility panel is considered **investigational** for all other indications.

3. Hereditary gastrointestinal/colorectal cancer susceptibility panel targeted mRNA sequencing analysis for the interpretation of variants of unknown significance is considered **investigational** because it is typically either considered an existing component of the genetic testing process for quality assurance or follow up testing without proven utility.

NOTE: If a multigene cancer panel is performed, the appropriate panel code should be used.

Rationale and References

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/genetics_ceg.pdf

This guideline outlines criteria for assessment for hereditary colorectal syndromes as follows: Polyposis: Patient with a personal history of, or a single family member with, at least 10 adenomatous polyps, at least 2 hamartomatous polyps, or at least 5 serrated polyps/lesions proximal to the rectum (p. HRS-1) Individuals meeting LS testing criteria (p. HRS-1, HRS-3, LS-1) (see MLH1, MSH2, MSH6, PMS2, EPCAM Sequencing and/or Deletion/Duplication Analysis).

NCCN also states that the CRC-risk associated genes to include in germline multigene panel testing are as follows: APC, BMPR1A, EPCAM, MUTYH, MLH1, MSH2, MSH6, PMS2, PTEN, SMAD4, STK11, and TP53 (p. HRS-A 2 of 3).

Some individuals will have variants of uncertain significance (VUS); post-test counseling should include considering referral to research studies for the purpose of learning the functional impact of VUSs such as variant reclassification programs through clinical labs or registries (p. EVAL-A 8 of 9).

Definitions

N/A

Hereditary Polyposis Susceptibility Panels

A hereditary polyposis panel includes genes that are associated with inherited susceptibility to colon polyposis.

1. Genetic testing using a hereditary polyposis susceptibility panel is considered **medically necessary** when the member meets **BOTH** A and B:

    1. The member has a history of any of the following:

        1. 10 or more cumulative adenomas, **OR**

        2. Congenital hypertrophy of the retinal pigment epithelium (CHRPE), **OR**

        3. Desmoid tumor, **OR**

        4. Hepatoblastoma, **OR**

        5. Cribriform-morular variant of papillary thyroid cancer, **OR**

        6. A clinical diagnosis of serrated-polyposis syndrome, with at least some adenomas, based on one of the following:

            1) 5 or more serrated polyps proximal to the rectum, all being 5mm or greater in size and at least 2 being 10mm or greater in size, **OR**

            2) More than 20 serrated polyps of any size distributed throughout the large bowel, with at least 5 or more being proximal to the rectum, **AND**

    2. The panel includes, at a minimum, sequencing of the following genes: *APC* and *MUTYH*.

2. Genetic testing using a hereditary polyposis susceptibility panel is considered **investigational** for all other indications.

3. mRNA sequencing analysis in genes associated with polyposis syndromes for the interpretation of variants of unknown significance is considered **investigational** because it is typically either considered an existing component of the genetic testing process for quality assurance or follow up testing without proven utility.

Rationale and References

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/genetics_ceg.pdf

This guideline outlines scenarios in which individuals meet criteria for germline genetic testing for "all polyposis and [colorectal cancer] genes" (p.POLYP-1A). These include: personal history of 10-20 cumulative adenomas, congenital hypertrophy of retinal pigment epithelium (CHRPE), desmoid tumor, hepatoblastoma, cribriform-morular variant of papillary thyroid cancer, and clinically diagnosed serrated polyposis syndrome if adenomas are present (p. POLYP-1).

This guideline also notes that some individuals with a clinical diagnosis of serrated polyposis syndrome (defined as 5 or more serrated polyps proximal to the rectum all being 5mm or larger with 2 or more being 10 or more mm in size, or more than 20 serrated polyps of any size distributed throughout the colon, with 5 or more being proximal to the rectum) may carry pathogenic variants in MUTYH (biallelic) or RNF43 (monoallelic) (p. SPS-1).

Some individuals will have variants of uncertain significance (VUS); post-test counseling should include considering referral to research studies for the purpose of learning the functional impact of VUSs such as variant reclassification programs through clinical labs or registries (p. EVAL-A, 8 of 9).

Definitions

N/A

Inflammatory Bowel Disease / Crohn's Disease Prognostic Algorithmic Tests

1. Inflammatory bowel disease / Crohn’s disease prognostic algorithmic tests are considered **investigational** for all indications.

Rationale and References

Concert Evidence Review for Coverage Determination. Inflammatory Bowel Disease/Crohn’s Prognostic Algorithmic Tests. Published 06/01/2025.

This review focused on peer-reviewed, published evidence of the clinical utility and validity of the Prometheus Crohn’s Prognostic test from May 12, 2024 through May 12, 2025. A total of 5 full text publications were reviewed. Although none technically met the formal inclusion criteria, one international (UK) study was identified and included in this evidence review given the strength of the study type (randomly controlled trial) and the fact that it directly addresses the question of clinical utility for these tests. In this 2024 multicenter randomly controlled trial, researchers compared two treatment strategies for individuals with newly diagnosed Crohn’s disease. They stratified patients into two different treatment groups using the 17-gene blood-based biomarker assay (PredictSURE-IBD). Ultimately, they determined that the biomarker test results did not significantly influence treatment outcomes and the study concluded that the biomarker did not show clinical utility (Noor, et al).

At this time, there are no changes to existing guidelines, and there were no new professional society guidelines to include in the evidence review.

There is INSUFFICIENT EVIDENCE in peer-reviewed publications to support the clinical validity and utility of Crohn’s Prognostic Algorithmic tests to effectively result in improved health outcomes compared to the current standard of care. At this time, the current evidence does not support health plan coverage due to a lack of evidence that prognostic serological IBD testing results in better outcomes than the current treatments.

Definitions

N/A

Inflammatory Bowel Disease / Crohn's Disease Diagnostic Algorithmic Tests

1. Inflammatory bowel disease / Crohn’s disease diagnostic algorithmic tests are considered **investigational** for all indications.

Rationale and References

Concert Evidence Review for Coverage Determination. Inflammatory Bowel Disease/Crohn’s Diagnostic Algorithmic Tests. Published 06/01/2025.

This review focused on identification of peer-reviewed, published evidence of the clinical validity and utility of Prometheus IBD sgi Diagnostic from May 13, 2024 through May 13, 2025. A total of 5 full text publications were reviewed and none met the inclusion criteria.

At this time, there are no changes to existing guidelines, and there were no new professional society guidelines or peer-reviewed literature identified to include in the evidence review.

There is INSUFFICIENT EVIDENCE in peer-reviewed publications to support the clinical validity and utility of IBD Crohn’s Diagnostic Algorithmic tests, such as Prometheus IBD sgi Diagnostic, to effectively result in improved health outcomes compared to the current standard of care. At this time, the available evidence does not support health plan coverage of these tests.

Definitions

N/A

Lung Cancer Focused Molecular Profiling Panels

1. Lung cancer focused molecular profiling panels are considered **medically necessary** when:

    1. The member has a diagnosis of:

        1. Advanced (stage IIIb or higher) or metastatic lung adenocarcinoma, **OR**

        2. Advanced (stage IIIb or higher) or metastatic large cell lung carcinoma, **OR**

        3. Advanced (stage IIIb or higher) or metastatic squamous cell lung carcinoma, **OR**

        4. Advanced (stage IIIb or higher) or metastatic non-small cell lung cancer (NSCLC) not otherwise specified (NOS), **AND**

    2. The member is seeking further cancer treatment (e.g., therapeutic chemotherapy).

2. Repeat lung cancer-focused molecular profiling panels are considered **medically necessary** when the member has progression on targeted therapy for non-small cell lung cancer.

3. Lung cancer-focused molecular profiling panels are considered **investigational** for all other indications.

NOTE: If a panel is performed, appropriate panel codes should be used.

Rationale and References

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer 8.2025
https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

This guideline recommends molecular testing for patients with advanced or metastatic disease and when feasible, testing should be performed via a broad, panel-based approach, most typically performed by NGS. This can be a single assay, combination of assays, or tiered approach (p. NSCL-19).

Additionally, patients with stages IB-IIIA or IIIB [T3,N2] are recommended to have testing for PD-L1, EGFR and ALK if perioperative systemic therapy is being considered (p. NSCL-E 1 of 6). In some clinical scenarios it is necessary to do rapid testing which can be followed up with broad testing (p. NSCL-H 1 of 8, NSCL-H 2 of 8).

NCCN discusses re-testing tumor tissue in patients with progression who are receiving targeted therapy. This applies to all molecular targets associated with lung cancer and is warranted given it could aid in treatment decision-making (NSCL-H 7 of 8).

Definitions

1. **Advanced** cancer (advanced stages or advanced tumor or advanced/metastatic): Cancer that is unlikely to be cured or controlled with treatment. The cancer may have spread from where it first started to nearby tissue, lymph nodes, or distant parts of the body. Treatment may be given to help shrink the tumor, slow the growth of cancer cells, or relieve symptoms.
2. **Advanced** cancer (advanced stages or advanced tumor or advanced/metastatic) is unlikely to be cured or controlled with treatment. The cancer may have spread from where it first started to nearby tissue, lymph nodes, or distant parts of the body. Treatment may be given to help shrink the tumor, slow the growth of cancer cells, or relieve symptoms.

Lung Cancer Focused Panel Tests via Circulating Tumor DNA (ctDNA)

1. Lung cancer focused panel tests via circulating tumor DNA (ctDNA) are considered **medically necessary** when:

    1. The member has a new diagnosis or progression of any of the following:

        1. Advanced or metastatic lung adenocarcinoma, **OR**

        2. Advanced or metastatic large cell lung carcinoma, **OR**

        3. Advanced or metastatic squamous cell lung carcinoma, **OR**

        4. Advanced or metastatic non-small cell lung cancer (NSCLC) not otherwise specified (NOS).

2. Lung cancer focused panel tests via circulating tumor DNA (ctDNA) are considered **investigational** for all other indications.

Rationale and References

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer 8.2025
https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

This guideline recommends biomarker testing be performed pre-treatment for patients with clinically confirmed advanced or metastatic disease of the following lung cancer pathologies: adenocarcinoma, large cell, squamous cell carcinoma, and non-small cell lung cancer not otherwise specified (p. NSCL-14, NSCL-15, NSCL-19, NSCL-H 2-7 of 8). Broad NGS panel-based testing is recommended over other modalities and smaller tests where feasible (NSCL-H, 2 of 8). Tissue-based testing and ctDNA both have high specificity and false negative rates and therefore can be used together to reduce turnaround time and increase the likelihood of finding actionable targets, however, ctDNA should not be used outside of advanced or metastatic disease (NSCL-H

8 of 8). In patients who have progressed following targeted therapy, NCCN recommends consideration of biomarker analysis to evaluate possible mechanisms of resistance (p. NSCL-H, 7 of 8).

Definitions

1. **Advanced** cancer (advanced stages or advanced tumor or advanced/metastatic): Cancer that is unlikely to be cured or controlled with treatment. The cancer may have spread from where it first started to nearby tissue, lymph nodes, or distant parts of the body. Treatment may be given to help shrink the tumor, slow the growth of cancer cells, or relieve symptoms.
2. **Advanced** cancer (advanced stages or advanced tumor or advanced/metastatic) is unlikely to be cured or controlled with treatment. The cancer may have spread from where it first started to nearby tissue, lymph nodes, or distant parts of the body. Treatment may be given to help shrink the tumor, slow the growth of cancer cells, or relieve symptoms.
3. **Circulating tumor DNA (ctDNA)** is fragmented, tumor-derived DNA circulating in the bloodstream that is not being carried in a cell. ctDNA derives either directly from the tumor or from circulating tumor cells.

Mitochondrial Genome Sequencing, Deletion/Duplication, and/or Nuclear Gene Panel

1. Mitochondrial genome sequencing, deletion/duplication, and/or nuclear genes analysis to establish or confirm a diagnosis of a primary mitochondrial disorder is considered **medically necessary** when:

    1. The member has a classic phenotype of one of the maternally inherited syndromes (e.g., Leber hereditary optic neuropathy, mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes [MELAS], myoclonic epilepsy with ragged red fibers [MERRF], maternally inherited deafness and diabetes [MIDD], neuropathy, ataxia, retinitis pigmentosa [NARP], Kearns-Sayre syndrome/CPEO); or of a nuclear DNA mitochondrial disorder (e.g., mitochondrial neurogastrointestinal encephalopathy [MNGIE]); **OR**

    2. The member has non-specific clinical features suggestive of a primary mitochondrial disorder and meets **ALL** of the following:

        1. Clinical findings of at least two of the following:

            1) Ptosis, **OR**

            2) External ophthalmoplegia, **OR**

            3) Proximal myopathy, **OR**

            4) Exercise intolerance, **OR**

            5) Cardiomyopathy, **OR**

            6) Sensorineural deafness, **OR**

7) Optic atrophy, **OR**

8) Pigmentary retinopathy, **OR**

9) Diabetes mellitus, **OR**

10) Fluctuating encephalopathy, **OR**

11) Seizures, **OR**

12) Dementia, **OR**

13) Migraine, **OR**

14) Stroke-like episodes, **OR**

15) Ataxia, **OR**

16) Spasticity, **OR**

17) Chorea, **OR**

18) Multiple late term pregnancy losses, **AND**

2. Conventional biochemical laboratory studies have been completed and are non-diagnostic, including at least: plasma or CSF lactic acid concentration, ketone bodies, plasma acylcarnitines, and urinary organic acids, **AND**

3. Additional diagnostic testing indicated by the member's clinical presentation (e.g., fasting blood glucose, electrocardiography,

neuroimaging, electromyography, echocardiography, audiology, thyroid testing, electroencephalography, exercise testing) have been completed and are non-diagnostic.

2. Mitochondrial genome sequencing, deletion/duplication, and/or nuclear genes analysis to establish or confirm a diagnosis of a primary mitochondrial disorder is considered **investigational** for all other indications.

Rationale and References

Parikh S, Goldstein A, Koenig MK, et al. Diagnosis and management of mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society. Genet Med. 2015;17(9):689-701. doi:10.1038/gim.2014.177

In 2015, the Mitochondrial Medicine Society published the following consensus recommendations for DNA testing for mitochondrial disorders:

Massively parallel sequencing/NGS of the mtDNA genome is the preferred methodology when testing mtDNA and should be performed in cases of suspected mitochondrial disease instead of testing for a limited number of pathogenic point mutations. Patients with a strong likelihood of mitochondrial disease because of a mtDNA mutation and negative testing in blood, should have mtDNA assessed in another tissue to avoid the possibility of missing tissue-specific mutations or low levels of heteroplasmy in blood; tissue-based testing also helps assess the risk of other organ involvement and heterogeneity in family members and to guide genetic counseling. Heteroplasmy analysis in urine can selectively be more informative and accurate than testing in blood alone, especially in cases of MELAS due to the common m. 3243A>G mutation. mtDNA deletion and duplication testing should be performed in cases of suspected mitochondrial disease via NGS of the mtDNA genome, especially in all patients undergoing a diagnostic tissue biopsy. If a single small deletion is identified using polymerase chain reaction–based analysis, then one should be cautious in associating these findings with a primary mitochondrial disorder. When multiple mtDNA deletions are noted, sequencing of nuclear genes involved in mtDNA

biosynthesis is recommended. When a tissue specimen is obtained for mitochondrial studies, mtDNA content (copy number) testing via real-time quantitative polymerase chain reaction should strongly be considered for mtDNA depletion analysis because mtDNA depletion may not be detected in blood. mtDNA proliferation is a nonspecific compensatory finding that can be seen in primary mitochondrial disease, secondary mitochondrial dysfunction, myopathy, hypotonia, and as a by-product of regular, intense exercise. When considering nuclear gene testing in patients with likely primary mitochondrial disease, NGS methodologies providing complete coverage of known mitochondrial disease genes is preferred. Single-gene testing should usually be avoided because mutations in different genes can produce the same phenotype. If no known mutation is identified via known NGS gene panels, then whole exome sequencing should be considered (p. 692-693).

Chinnery PF. Primary Mitochondrial Disorders Overview. 2000 Jun 8 [Updated 2021 Jul 29]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1224/

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online.

Their recommendations are as follows:

Common clinical features of mitochondrial disorders include: ptosis external ophthalmoplegia proximal myopathy exercise intolerance cardiomyopathy sensorineural deafness optic atrophy pigmentary retinopathy diabetes mellitus fluctuating encephalopathy seizures dementia migraine stroke-like episodes ataxia spasticity chorea high incidence of mid- and late-pregnancy loss

When a patient's clinical picture is nonspecific but highly suggestive of a mitochondrial disorder, the clinician should start with measurement of plasma or CSF lactic acid concentration, ketone bodies, plasma acylcarnitines, and urinary organic acids.

Traditionally, the diagnosis of mitochondrial disorders has been based on demonstrating mitochondrial dysfunction in a relevant tissue biopsy (e.g., a skeletal muscle or liver biopsy, or skin fibroblasts), with the particular pattern of biochemical abnormality being used to direct targeted molecular genetic testing of mtDNA, specific nuclear genes, or both. However, the more widespread availability of molecular diagnostic techniques and the advent of exome and genome sequencing has changed the diagnostic approach.

One important caveat arises from the fact that many mtDNA pathogenic variants are heteroplasmic, and the proportion of mutated mtDNA in blood may be undetectable. This can be circumvented by analyzing mtDNA from another tissue – typically skeletal muscle or urinary epithelium – in which the level of heteroplasmy tends to be higher. Some common mtDNA pathogenic variants (e.g., large-scale deletions causing CPEO) may only be detected in skeletal muscle.

In individuals with a specific clinical phenotype (e.g., MELAS, LHON, POLG-related disorders), it may be possible to reach a diagnosis with targeted analysis of specific mtDNA pathogenic variants or single-gene testing of a nuclear gene.

A mitochondrial disorder multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype.

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. Such testing includes exome sequencing, genome sequencing, and mitochondrial sequencing which can simultaneously analyze nuclear DNA and mtDNA.

Definitions

1. **Genome Sequencing (GS)** is a genomic technique for sequencing the complete DNA sequence, which includes protein coding as well as non-coding DNA elements.

2. **Mitochondrial disorder** refers to a heterogenous group of disorders caused by dysfunctional mitochondria, the organelles responsible for oxidative phosphorylation within the cell.
3. **Mitochondrial genome sequencing** analyses the genomic material located in the cell's mitochondria, the organelles responsible for oxidative phosphorylation within the cell.

MLH1, MSH2, MSH6, PMS2, and/or EPCAM Sequencing and/or Deletion/Duplication Analysis

I. Lynch syndrome panels, *MLH1*, *MSH2*, *MSH6*, *PMS2*, and/or *EPCAM* sequencing and/or duplication analysis for Lynch syndrome/HNPCC is considered **medically necessary** when:

A. The member has a tumor that shows evidence of mismatch repair (MMR) deficiency (either by microsatellite instability (MSI) or loss of MMR protein expression), **OR**

B. The member has a diagnosis of a Lynch syndrome-related cancer (colorectal, endometrial, gastric, ovarian, pancreatic, urothelial, brain (usually glioblastoma), biliary tract, small intestinal, sebaceous adenoma, sebaceous carcinoma, or keratoacanthoma), **AND** any of the following:

1. Diagnosed before age 50, **OR**

2. Diagnosed at any age with an additional Lynch syndrome-related cancer, **OR**

3. Diagnosed at any age with one or more first- or second-degree relatives diagnosed before age 50 with a Lynch syndrome-related cancer, **OR**

4. Diagnosed at any age with two or more first- or second-degree relatives diagnosed at any age with a Lynch syndrome-related cancer, **OR**

C. The member has a family history of **any** of the following:

1. One or more first-degree relatives diagnosed with colorectal or endometrial cancer before age 50, **OR**

2. One or more first- or second-degree relatives diagnosed with colorectal or endometrial cancer and an additional Lynch syndrome-related cancer, **OR**

3. Two or more first- or second-degree relatives on the same side of the family diagnosed with a Lynch syndrome-related cancer, one of whom was diagnosed before age 50, **OR**

4. Three or more first- or second-degree relatives on the same side of the family diagnosed with a Lynch syndrome-related cancer, **OR**

D. The member has a 5% or greater risk of having Lynch syndrome based on one of the following variant prediction models: MMRpro, PREMM5, MMRpredict, **OR**

E. The member has a personal history of colorectal and/or endometrial cancer with a PREMM5 score of 2.5% or greater.

II. Lynch syndrome panels, *MLH1*, *MSH2*, *MSH6*, *PMS2*, and/or *EPCAM* sequencing and/or duplication analysis for Lynch syndrome/HNPCC is considered **investigational** for all other indications.

III. *MLH1, MSH2, MSH6, PMS2* and *EPCAM* mRNA sequencing analysis for the interpretation of variants of unknown significance is considered **investigational** because it is typically either considered an existing component of the genetic testing process for quality assurance, or follow up testing without proven utility.

Rationale and References

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/genetics_ceg.pdf

This guideline outlines testing criteria for the evaluation of Lynch syndrome. These criteria include: An individual with a Lynch-syndrome (LS)-related cancer (colorectal, endometrial, gastric, ovarian, pancreatic, urothelial, brain (usually glioblastoma), biliary tract, and small intestine, as well

as sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas) and any of the following: Diagnosed younger than 50 years A synchronous or metachronous LS-related cancer regardless of age 1 first-degree or second-degree relative with an LS-related cancer diagnosed younger than 50 years 2 or more first-degree or second-degree relatives with an LS-related cancer regardless of age Family history of any of the following At least 1 first-degree relative with a colorectal or endometrial cancer diagnosed younger than 50 years At least 1 first- or second-degree relative with a colorectal or endometrial cancer and a synchronous or metachronous LS-related cancer regardless of age 2 or more first-degree or second-degree relatives with LS-related cancers, one of whom was diagnosed before age 50 3 or more first-degree or second-degree relatives with LS-related cancers regardless of age An individual with a 5% risk or greater of having an MMR gene pathogenic variant based on predictive models (i.e., PREMM5, MMRpro, MMRpredict) An individual with a personal history of CRC and/or endometrial cancer with a PREMM5 score of 2.5% or greater. A personal history of mismatch repair deficiency in any solid tumor

Some individuals will have variants of uncertain significance (VUS); post-test counseling should include considering referral to research studies for the purpose of learning the functional impact of VUSs such as variant reclassification programs through clinical labs or registries (p. HRS-3 and EVAL-A 8 of 9).

Definitions

1. **First-degree relatives** are parents, siblings, and children.
2. **Lynch syndrome-related cancer** is defined as any of the following cancer types: colorectal, endometrial, gastric, ovarian, pancreatic, urothelial, brain (usually glioblastoma), biliary tract, small intestinal, sebaceous adenoma, sebaceous carcinoma, or keratoacanthoma.
3. **Second-degree relatives** are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half siblings.

Noonan Spectrum Disorders/RASopathies Multigene Panel

1. The use of a multigene panel to confirm or establish a diagnosis of a Noonan spectrum disorder/RASopathy (e.g., Noonan syndrome, Legius syndrome, Costello syndrome, Cardio-facial-cutaneous syndrome, NF1, Noonan-like syndrome) is considered **medically necessary** when:

    1. The member has at least one of the following:

        1. Characteristic facies (low-set, posteriorly rotated ears with fleshy helices, vivid blue or blue-green irises, widely spaced, down slanted eyes, epicanthal folds, ptosis), **OR**

        2. Short stature, **OR**

        3. Congenital heart defect (most commonly pulmonary valve stenosis, atrial septal defect, and/or hypertrophic cardiomyopathy), **OR**

        4. Developmental delay, **OR**

        5. Broad or webbed neck, **OR**

        6. Unusual chest shape with superior pectus carinatum, inferior pectus excavatum, **OR**

        7. Widely spaced nipples, **OR**

        8. Cryptorchidism in males, **OR**

        9. Lentigines, **OR**

        10. Café au lait macules.

2. The use of a multigene panel to confirm or establish a diagnosis of a Noonan spectrum disorder/RASopathy (e.g., Noonan syndrome, Legius syndrome, Costello syndrome, Cardio-facial-cutaneous syndrome, NF1, Noonan-like syndrome) is considered **investigational** for all other indications.

Rationale and References

Rauen KA. The RASopathies. Annu Rev Genomics Hum Genet. 2013;14:355-369. doi:10.1146/annurev-genom-091212-153523

Per the NIH, the RASopathies are comprised of the following conditions: neurofibromatosis type 1, Noonan syndrome, Noonan syndrome with multiple lentigines, capillary malformation–arteriovenous malformation syndrome, Costello syndrome, cardio-facio-cutaneous syndrome, and Legius syndrome.

Roberts AE. Noonan Syndrome. 2001 Nov 15 [Updated 2025 Jun 5]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1124/

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online.

It is recommended that diagnostic testing for Noonan Spectrum Disorders via multigene panel be performed as follows:

Noonan syndrome (NS) should be suspected in individuals with the following clinical, laboratory, and family history findings. Characteristic facies. The facial appearance of NS shows considerable change with age, being most striking in young and middle childhood, and most subtle in adulthood. Key features found regardless of age include the following: Low-set, posteriorly rotated ears with fleshy helices Vivid blue or blue-green irises Widely spaced and down slanted

palpebral fissures Epicanthal folds Fullness or drooping of the upper eyelids (ptosis) Short stature for sex and family background Congenital heart defects, most commonly pulmonary valve stenosis, atrial septal defect, and/or hypertrophic cardiomyopathy Developmental delay of variable degree Broad or webbed neck Unusual chest shape with superior pectus carinatum and inferior pectus excavatum Widely spaced nipples Cryptorchidism in males Lymphatic dysplasia of the lungs, intestines, and/or lower extremities

When the phenotypic findings suggest the diagnosis of Noonan Syndrome (NS), molecular genetic testing approaches usually include the use of a multi-gene panel testing as it is more efficient and cost effective than serial single-gene testing. Approximately 50% of individuals with NS have a pathogenic missense variant in PTPN11; therefore, single-gene testing starting with PTPN11 would be the next best first test.

Definitions

1. **Developmental delay** (DD) is defined as slow-to-meet or not reaching milestones in one or more of the areas of development (communication, motor, cognition, social-emotional, or adaptive skills) in the expected way for a child's age.

Ovarian Cancer Treatment Algorithmic Tests

1. Ovarian cancer treatment algorithmic tests are considered **medically necessary** when:
    1. The member has a diagnosis of ovarian cancer, **AND**
    2. The member is being considered for PARP inhibitor therapy.
2. Ovarian cancer treatment algorithmic tests are considered **investigational** for all other indications.

Rationale and References

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer 3.2025
https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf

This guideline recommends molecular analysis for alterations that might impact clinical decision making. This testing should include BRCA1/2 status, as there are specific post primary treatment recommendations based on BRCA1/2 status (OV-1, 2, 3, and 5; OV-B 1 of 3).

Tew WP, Lacchetti C, Ellis A, et al. PARP Inhibitors in the Management of Ovarian Cancer: ASCO Guideline. J Clin Oncol. 2020;38(30):3468-3493. doi:10.1200/JCO.20.01924

In 2020, ASCO issued a guideline for the use of PARP inhibitors in the management of ovarian cancer, which they updated via a targeted literature review in 2022. Per their updated recommendations, PARPi maintenance therapy “should be offered” to all patients with newly diagnosed stage III-IV EOC (epithelial ovarian, tubal, or primary peritoneal cancer, high-grade serous or endometrioid type), whose disease is in complete or partial response to first-line, platinum-based chemotherapy (p. 3879).

Tew WP, Lacchetti C, Kohn EC; PARP Inhibitors in the Management of Ovarian Cancer Guideline Expert Panel. Poly(ADP-Ribose) Polymerase Inhibitors in the Management of Ovarian Cancer: ASCO Guideline Rapid Recommendation Update. J Clin Oncol. 2022;40(33):3878-3881. doi:10.1200/JCO.22.01934

Definitions

N/A

Pan-Cancer Hereditary Cancer Susceptibility Panels

A pan-cancer hereditary cancer susceptibility panel includes genes that are associated with inherited susceptibility to several different types of cancer (e.g., breast cancer, colon cancer, stomach cancer, etc.).

I. Genetic testing using a pan-cancer hereditary cancer susceptibility panel is considered **medically necessary** when the member meets **BOTH** A and B:

A. The member has one of the following:

1. A personal history, or a close relative with a personal history, of one of the following cancers ≤ 50 years of age:

a) Breast cancer, **OR**

b) Colorectal cancer, **OR**

c) Endometrial cancer, **OR**

2. The member has a personal history of one of the following:

a) Pancreatic cancer at any age, **OR**

b) Metastatic prostate cancer at any age, **OR**

c) Ovarian, peritoneal, or fallopian tube cancer at any age, **OR**

3. The member's personal or family history is suspicious for more than one hereditary cancer syndrome, **AND**

B. The panel includes, at a minimum, sequencing of the following genes: *BRCA1*, *BRCA2*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *PMS2*.

II. Genetic testing using a pan-cancer hereditary cancer susceptibility panel is considered **investigational** for all other indications.

III. Hereditary cancer susceptibility panel targeted mRNA sequencing analysis for the interpretation of variants of unknown significance is considered **investigational** because it is typically either considered an existing component of the genetic testing process for quality assurance or follow up testing without proven utility.

NOTE: If a multigene cancer panel is performed, the appropriate panel code should be used.

Rationale and References

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate 2.2026 https://www.nccn.org/professionals/physician_gls/pdf/genetics_bopp.pdf

Germline genetic testing is recommended for patients with breast cancer diagnosed at age 50 years or younger (p. CRIT-2) and metastatic prostate cancer diagnosed at any age (p. CRIT-6).

This guideline defines multigene testing as analysis of a set of genes that are associated with one or more cancer phenotypes in a family. NCCN states that in some families, there is suspicion for more than one hereditary cancer syndrome. In those cases, phenotype-directed testing via a “tailored multigene panel” is a more efficient and cost-effective method of testing. They state that “intermediate penetrant (moderate-risk) genes” may also be included in the multigene panels (p. EVAL-A 3 of 11).

These guidelines also recommend consideration of RNA studies to further define the meaning of variants of unknown significance. Research studies designed to explore the functional impact of variants, such as variant reclassification programs through clinical labs or registries, should be considered (p. EVAL-A, 9 of 11).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/genetics_ceg.pdf

This guideline recommends germline multigene panel testing in individuals with a personal history of colorectal cancer who are under age 50 at diagnosis as well as for other Lynch-syndrome related cancers, including ovarian and pancreatic cancer (p. HRS-3). Test selection should include at a minimum selected genes associated with colorectal cancer risk but additional genes can be included based on a patient's personal and family history of cancer (p. HRS-A, 2 of 3).

Use of Multi-Gene Panel Testing. Position Statement from National Society of Genetic Counselors. https://www.nsgc.org/Policy-Research-and-Publications/Position-Statements/Position-Statements/Post/use-of-multi-gene-panel-tests. Released March 14, 2017. Reaffirmed 2020 and 2023.

The National Society of Genetic Counselors released a position statement (Adopted 2017, reaffirmed 2020 and 2023) endorsing the use of multigene panels when clinically warranted and appropriately applied, stating the following:

These tests can provide a comprehensive and efficient route to identifying the genetic causes of disease. Before ordering a multi-gene panel test, providers should thoroughly evaluate the analytic and clinical validity of the test, as well as its clinical utility. Additional factors to consider include, but are not limited to: clinical and family history information, gene content of the panel, limitations of the sequencing and informatics technologies, and variant interpretation and reporting practices.

Panels magnify the complexities of genetic testing and underscore the value of experts, such as genetic counselors, who can educate stakeholders about appropriate utilization of the technology to mitigate risks of patient harm and unnecessary costs to the healthcare system. NSGC supports straightforward and transparent pricing so that patients, providers, laboratories, and health plans can easily weigh the value of genetic testing in light of its cost.

Tung N, Ricker C, Messersmith H, et al. Selection of Germline Genetic Testing Panels in Patients With Cancer: ASCO Guideline. J Clin Oncol. 2024;42(21):2599-2615. doi:10.1200/JCO.24.00662

ASCO released guidelines in 2024 regarding appropriate use of multigene panel germline testing for individuals with cancer. As part of the guideline, they recommend germline genetic testing via a multigene panel for patients with cancer who have suspicion for more than one gene related to that cancer type (Table 4, p. 2605). Several genes are listed in Table 1 (p. 2603), which they recommend be included for specific populations of people with cancer (Table 4, p. 2605).

Definitions

1. **Breast cancer** is a term that applies to patients with invasive cancer or ductal carcinoma in situ (DCIS).

Pharmacogenetic Panel Tests - Alternate

1. Pharmacogenetic panel tests are considered **medically necessary** when:
    1. The member is age 18 years or older, **AND**
    2. The member has previously been treated with at least one medication related to their diagnosis that was ineffective, **AND**
    3. The member is being considered for one or more specific medication(s) related to their diagnosis that is known to have a gene-drug interaction, **AND**
    4. The pharmacogenetic panel test being considered has proven clinical validity, as demonstrated through independent evaluation from a recognized third-party source, including but not limited to MolDx, ECRI, Hayes, Optum Genomics or FDA, **AND**
    5. The member has a diagnosis of any of the following for which a treatment is being considered:
        1. Major depressive disorder, **OR**
        2. Generalized anxiety disorder.
2. Pharmacogenetic panel tests are considered **investigational** for all other indications, including:
    1. As an initial screening test for medication selection.

Rationale and References

Bunka M, Wong G, Kim D, et al. Evaluating treatment outcomes in pharmacogenomic-guided care for major depression: A rapid review and meta-analysis. Psychiatry Res. 2023;321:115102. doi:10.1016/j.psychres.2023.115102

In their 2023 rapid review and meta-analysis, Bunka, et al. discuss the age of patients who have participated in studies related to the use of pharmacogenetic panels. The authors note that there is currently insufficient evidence to support ordering PGx tests for adolescents as a part of their treatment for depression (p. 5).

Centers for Medicare & Medicaid Services. Medicare Coverage Database: Local Coverage Determination. MolDX: Phenotypic Biomarker Detection in Circulating Tumor Cells (L38294). Revision Effective October 2, 2025.
https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=38294&ver=24&=

The CMS local coverage determination (LCD) entitled "MolDX: Pharmacogenomics Testing" states the following: "PGx tests are indicated when medications are being considered for use (or already being administered) that are medically necessary, appropriate, and approved for use in the patient's condition and are known to have a gene(s)-drug interaction that has been demonstrated to be clinically actionable…"

Definitions

2. **Clinical validity,** according to the National Institutes of Health-Department of Energy (NIH-DOE) Task Force on Genetic Testing, describes the accuracy with which a test identifies a particular clinical condition. The components of measuring clinical validity are:

    1. **Sensitivity**: among people with a specific condition, the proportion who have a positive test result

    2. **Specificity**: among people who do not have the condition, the proportion who have a negative test result

    3. **Positive predictive value**: among people with a positive test result, the proportion of people who have the condition

4. **Negative predictive value**: among people with a negative test result, the proportion who do not have the condition

Post Heart Transplant Gene Expression Panels for Rejection Risk via Peripheral Blood

1. The use of post heart transplant gene expression panels for rejection risk via peripheral blood to determine management of patients after heart transplantation is considered **medically necessary** when:

    1. The member is age 18 or older, **AND**

    2. The member has undergone heart transplant, **AND**

    3. The member is at low-risk for organ rejection, **AND**

    4. The member's heart transplant was performed at least 2 months ago and less than 5 years ago.

2. The use of post heart transplant gene expression panels for rejection risk via peripheral blood to determine management of patients after heart transplantation is considered **investigational** for all other indications.

Rationale and References

Velleca A, Shullo MA, Dhital K, et al. The International Society for Heart and Lung Transplantation (ISHLT) guidelines for the care of heart transplant recipients. J Heart Lung Transplant. 2023;42(5):e1-e141. doi:10.1016/j.healun.2022.10.015

The ISHLT guidelines for the care of heart transplant patients (2023) include recommendations for the non-invasive monitoring of acute cellular rejection (ACR) after heart transplant (HT). They specifically address Allomap and state that peripheral blood testing "can be used in low-risk patients between 2 months and 5 years after HT to identify adult recipients who have low risk of current ACR to reduce the frequency of EMB [endomyocardial biopsy]". At this time, the recommendation is specific to adults given data in children does not allow for a general recommendation for GEP (p. e38).

Definitions

1. **Low-risk for organ rejection** may include features such as lack of allosensitization (lack of anti-HLA antibodies in peripheral blood), older recipient age, more than one year after transplantation, male sex assigned at birth, and non-African American ancestry.

Prenatal Cell-free DNA Testing for Fetal Blood Group Genotyping

1. Prenatal cell-free DNA testing for fetal blood group genotyping is considered **medically necessary** when:

    1. The member is pregnant, **AND**

    2. The member is confirmed to have a positive antibody screen (ABSC) for an antibody or antibodies identified to be a clinically significant blood group antigen associated with hemolytic disease of the fetus and newborn[1], **AND**

    3. The member is not planning to undergo amniocentesis, **AND**

    4. There is documentation of an unknown or heterozygous genotype in the biological father of the fetus for the antigen to which the mother has been alloimmunized.

2. Prenatal cell-free DNA testing for fetal blood group genotyping is considered **investigational** for all other indications.

[1] **Clinically significant blood group antigen associated with hemolytic disease of the fetus and newborn** include those that have at least a moderate risk of disease and/or moderate severity. This includes antigens C, c, D, E, e, Fy^{a}, Fy^{b}, Jk^{a}, Jk^{b}, K, k, Kp^{a}, Kp^{b}, Js^{a}, Js^{b} and/or M. The remaining blood group antigens are thought to be low or no risk with mild severity.

Rationale and References

Mustafa HJ, Najjariasl P, Aghajani F, et al. Diagnostic accuracy of cell-free DNA for the determination of fetal red blood cell antigen genotype: a systematic review and meta-analysis. Am J Obstet Gynecol. 2025;233(5):428-445.e16. doi:10.1016/j.ajog.2025.05.004

A 2025 systematic review and meta-analysis analyzed 84 studies which assessed the fetal red blood cell antigen genotype using cell-free DNA. Seventy-six studies used polymerase chain reaction (PCR), 5 studies used next-generation sequencing (NGS), and three studies used

matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF). Antigens consisted of RhD, RhC, Rhc, RhE, Kell, and Duffy (Fya). The pooled sensitivity and specificity of this testing were both 99% across all studies. This analysis supports the high diagnostic accuracy of cell-free DNA testing for fetal blood group genotyping.

de Haas M, Thurik FF, Koelewijn JM, et al. Haemolytic disease of the fetus and newborn. Vox Sang. 2015;109(2):99-113. doi:10.1111/vox.12265

In the 2015 review "Haemolytic Disease of the Fetus and Newborn," the authors describe the pathophysiology of hemolytic disease of the newborn (HDFN) in which a mother is alloimmunized, creating antibodies against the corresponding antigen(s) carried on the fetal or newborn red blood cells. Only the IgG alloantibodies are actively transported across the placenta where they cause destruction of the fetal red blood cells when they bind to the corresponding antigen (p. 99-100).

Severity and risk of HDFN depends on multiple factors including immunoglobulin class, specificity of the maternal alloantibody, and intensity of antigen expression on the fetal red cells (occasionally present on other tissues as well). Based upon these factors, a majority of the over 400 blood group antigens are inappropriate candidates as causes of HDFN narrowing the antigens and alloantibodies of concern to a handful of blood groups including the following antigens: C, c, D, E, e, Fya, Fyb, Jka, Jkb, K, k, Kpa, Kpb, Jsa, Jsb and/or M. M is a special case as anti-M is commonly found in pregnant women, and while anti-M is typically an immunoglobulin M (IgM) antibody, it can manifest as an immunoglobulin G (IgG) antibody and produce a severe case of HDFN. The rest of the blood group antigens are low or no risk with mild severity and pose a much lower threat for the fetus and newborn. Noninvasive fetal genotyping can be a reliable method to identify these fetal antigens and monitor those at risk for the development of severe HDFN (p. 102-103).

Mustafa HJ, Sambatur EV, Shamshirsaz AA, et al. Monitoring and management of hemolytic disease of the fetus and newborn based on an international expert Delphi consensus. Am J Obstet Gynecol. 2025;232(3):280-300. doi:10.1016/j.ajog.2024.11.003

The 2024 publication titled "Monitoring and Management of Hemolytic Disease of the Fetus and Newborn Based on an International Expert Delphi Consensus" includes advice from an

international panel of experts spanning 25 countries and 6 continents who practice in fetal medicine, neonatology, and hematology. The consensus agreed that cfDNA should be used to determine fetal antigen status, particularly for the clinically significant antigens associated with hemolytic disease of the fetus and newborn such as the RhD, Kell, and Rhc antigens (p. 280).

Anti-M alloimmunization monitoring and workup of the fetus and newborn for the M antigen to include RBC phenotyping/molecular genotyping were included as necessary despite a consensus not being reached due to its role in hemolytic disease of the fetus and newborn. The authors noted it was vital for accurate diagnosis and management (p. 284).

Katri Haimila. Overview of non-invasive fetal blood group genotyping. Ann Blood. 2023;8(5). doi:10.21037/aob-21-41

In the 2023 publication “Overview of Non-invasive Fetal Blood Group Genotyping,” the author describes the cause of hemolytic disease of the fetus and newborn (HDFN) as being caused by maternal IgG antibodies crossing the placenta and binding to and attacking the fetal red blood cells. The antibodies that are specifically associated with this are anti-D as well as other Rh antibodies (anti-C, anti-c, anti-E, anti-e), Kell (anti-K, anti-k), anti-Fya (a Duffy antibody) and anti-Jka (a Kidd antibody). Anti-A and Anti-B from the ABO blood group are also capable of causing HDFN but pose their risk after birth.

When the mother has a clinically significant antibody (or antibodies) associated with HDFN and the father is heterozygous for the same blood group allele or father’s status is unknown, diagnostic fetal blood group genotyping is needed to determine the fetal risk involved. False negatives are a concern due to complicated blood group genetics and the abundance of maternal DNA inherent to the specimen, however advancements have been made and systems put in place to combat this providing highly accurate results. The use of special cfDNA preservative tubes and processing within a certain time frame are among the pre-analytical steps taken to improve accuracy and outcomes of testing. The fetal DNA fraction of the sample is relatively small already but reliability has been indicated as early as 9 to 12 weeks gestation. In the case of a negative in early pregnancy, repeat testing may be performed in a couple of weeks. The use of genetic blood group typing has taken the place of invasive procedures in pregnancies in which there are maternal antibodies associated with HDFN and has increased the health and wellbeing of both the mother and fetus (p. 1-4, 8).

Rego S, Ashimi Balogun O, Emanuel K, et al. Cell-Free DNA Analysis for the Determination of Fetal Red Blood Cell Antigen Genotype in Individuals With Alloimmunized Pregnancies. Obstet Gynecol. 2024;144(4):436-443. doi:10.1097/AOG.0000000000005692

In the 2024 publication "Cell-free DNA Analysis for the Determination of Fetal Red Blood Cell Antigen Genotype in Individuals With Alloimmunized Pregnancies," the authors support the use of cell-free fetal DNA testing for fetal red blood cell antigens and state the test is highly specific and sensitive in samples from alloimmunized pregnancies as early as 10 weeks of gestation citing their study of validation of next-generation sequencing based analysis of cell-free DNA. The validation showed a 100% specificity and sensitivity for the assay on 1,601 preclinical samples and 1,683 clinical samples with a specificity of 99.9%. 53 total clinical samples were compared to neonatal antigen typing performed by an independent laboratory with a 100% concordance between the results. The authors then extended the study to strengthen the support, including an additional 156 participants and their neonates in the US from 37 states with varied race and ethnic backgrounds and including four sets of twins. Again, the results were 100% concordance with neonatal results in comparison to the cell-free fetal antigen testing (p. 436-439).

The authors also mention the risks associated with the traditional method of approach to alloimmunized pregnancies, stating amniocentesis is the current standard. However, amniocentesis can lead to fetal loss or further strengthening of alloimmunization, putting the fetus at a greater risk which leads to the choice to not have the testing. In many cases, the fetal antigen status remains unknown whether by choice due to fear of fetal demise or poor uptake of the amniocentesis, exposing the fetus to further harm. Performing cell-free fetal DNA analysis provides a noninvasive alternative that is highly specific, sensitive, and mitigates the potentially unnecessary monitoring and invasive procedures, such as cordocentesis or intrauterine transfusions, that may follow. The authors also cited an average of $8,000 cost of care reduction by having cell-free fetal DNA testing (p. 440-442).

Definitions

1. **Amniocentesis** is a procedure in which a sample of amniotic fluid is removed from the uterus for prenatal diagnostic testing.

2. **Prenatal Cell-free DNA Testing** is a screening test that is used to determine the risk of specific genetic disorders by analyzing traces of cell-free DNA (cfDNA) in a pregnant woman's blood.

Prenatal Diagnosis via Exome Sequencing

1. Prenatal diagnosis, via amniocentesis, CVS, or PUBS, using exome sequencing may be considered **medically necessary** when:

    1. The member's current pregnancy has had a karyotype and/or microarray performed and the results were negative/normal, **AND**

    2. Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection, maternal condition), **AND**

    3. The member's current pregnancy has:

        1. Non-immune hydrops fetalis, **OR**

        2. Two or more major malformations on ultrasound, which are affecting different organ systems, **OR**

        3. The member's current pregnancy meets **BOTH** of the following:

            1) The current pregnancy has a:

                1) Skeletal anomaly, **OR**

                2) Central nervous system anomaly, **OR**

                3) Cardiac structural anomaly, **OR**

                4) Kidney or urinary tract anomaly, **AND**

            2) In cases where the identified anomaly is commonly associated with a specific genetic condition or specific group of conditions:

1) Targeted panel or single gene testing has been performed, **AND**

2) The results were negative/normal.

2. Prenatal diagnosis, via amniocentesis, CVS, or PUBS, using exome sequencing is considered **investigational** for all other indications.

Rationale and References

Monaghan KG, Leach NT, Pekarek D, Prasad P, Rose NC; ACMG Professional Practice and Guidelines Committee. The use of fetal exome sequencing in prenatal diagnosis: a points to consider document of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2020;22(4):675-680. doi:10.1038/s41436-019-0731-7

ACMG issued a statement on the use of fetal exome sequencing in prenatal diagnosis (2020) that included the following points to consider: “Exome sequencing may be considered for a fetus with ultrasound anomalies when standard CMA and karyotype analysis have failed to yield a definitive diagnosis. If a specific diagnosis is suspected, molecular testing for the suggested disorder (with single-gene test or gene panel) should be the initial test. At the present time, there are no data supporting the clinical use for ES for other reproductive indications, such as the identification of sonographic markers suggestive of aneuploidy or a history of recurrent unexplained pregnancy loss” (p. 676). “Pretest counseling is ideally provided by a genetics professional during which the types of variants that may be returned in a laboratory report for all tested family members would be reviewed” (p. 676). “With the use of prenatal ES, the turnaround time has to be rapid to maintain all aspects of reproductive choice. A rapid turnaround time has been demonstrated in the postnatal setting for critical genetic diagnoses in a pediatric and neonatal setting. Laboratories offering prenatal ES should have clearly defined turnaround times for this time-sensitive test” (p. 677). “Post-test counseling is recommended, regardless of the test result. It should be provided by individuals with relevant expertise, preferably a genetics professional” (p.

678). The statement also indicates that the detection rate of fetal anomalies is proportional to the severity of phenotype, with a range of 6% for fetuses with a single anomaly to 35% of fetuses with more than two anomalies (p. 676).

Al-Kouatly HB, Shivashankar K, Mossayebi MH, et al. Diagnostic yield from prenatal exome sequencing for non-immune hydrops fetalis: a systematic review and meta-analysis. Clin Genet. 2023;103(5):503-512. doi:10.1111/cge.14309

“We performed a systematic literature review and meta-analysis focusing specifically on ES in cases of NIHF to determine the contribution of monogenic etiologies” (p.504). “In our meta-analysis, greater than one-third (37%) of cases of NIHF with negative clinical workup for anemia, infections, and chromosomal disorders have a monogenic disorder detectable by ES providing clarification of etiological category (e.g., syndromic, neuromuscular, metabolic, etc.) and inheritance pattern (e.g., autosomal dominant de novo, autosomal dominant inherited, autosomal recessive, or X-linked)” (p. 507). “ES should be considered in the diagnostic workup of NIHF with and without associated ultrasound findings regardless of history of recurrence or consanguinity” (p. 503-504).

Mellis R, Oprych K, Scotchman E, Hill M, Chitty LS. Diagnostic yield of exome sequencing for prenatal diagnosis of fetal structural anomalies: A systematic review and meta-analysis. Prenat Diagn. 2022;42(6):662-685. doi:10.1002/pd.6115

A 2022 systematic review and meta-analysis conducted by Mellis et al. determined the diagnostic yield of prenatal whole-exome sequencing in the context of fetal anomalies and a normal chromosomal microarray analysis (CMA). Several single organ system phenotype groups had a statistically significantly higher diagnostic yield, including skeletal abnormalities, central nervous system anomalies, cardiac abnormalities, and CAKUT (congenital anomalies of the kidney and urinary tract) (p. 682).

Definitions

1. **Amniocentesis** is a procedure in which a sample of amniotic fluid is removed from the uterus for prenatal diagnostic testing.
2. **Exome Sequencing (ES)** is a genomic technique for sequencing all of the protein-coding regions of genes in the genome (also known as the exome).
3. **Major malformations** are structural defects that have a significant effect on function or appearance. They may be lethal or associated with possible survival with severe or moderate immediate or long-term morbidity. Examples by organ system include:
    - Genitourinary: renal agenesis (unilateral or bilateral), hypoplastic/cystic kidney
    - Cardiovascular: complex heart malformations (such as pulmonary valve stenosis, tetralogy of fallot, transposition of the great arteries, coarctation of the aorta, hypoplastic left heart syndrome
    - Musculoskeletal: osteochondrodysplasia/osteogenesis imperfecta, clubfoot, craniosynostosis, fetal growth restriction/intrauterine growth restriction (IUGR)
    - Central nervous system: anencephaly, hydrocephalus, myelomeningocele
    - Body wall: omphalocele/gastroschisis
    - Respiratory: cystic adenomatoid lung malformation

Prostate Cancer Treatment and Prognostic Algorithmic Tests

1. The use of a prostate cancer treatment and prognostic algorithmic test (i.e., Genomic Prostate Score Test, Prolaris, Decipher, ArteraAI) is considered **medically necessary** when:

    1. The member has a history of prostate cancer, **AND**

    2. The member has a life expectancy of 5 years or more, **AND**

    3. One of the following:

        1. The member has had radical prostatectomy, **AND**

            1) There is evidence of PSA recurrence or persistence, **OR**

        2. The member does **not** have low-risk prostate cancer, as defined by all of the following characteristics:

            1) cT1-cT2a, **AND**

            2) Grade Group 1, **AND**

            3) PSA <10 ng/ml.

2. The use of a prostate cancer treatment and prognostic algorithmic test is considered **investigational** for all other indications.

Rationale and References

Eggener SE, Rumble RB, Armstrong AJ, et al. Molecular biomarkers in localized prostate cancer: ASCO Guideline. J Clin Oncol. 2020;38(13):1474-1494. doi:10.1200/JCO.19.02768

ASCO issued a guideline called “Molecular Biomarkers in Localized Prostate Cancer: ASCO Guideline” (2020). The guideline overall states that tissue-based biomarker testing “may improve risk stratification,” but results should be interpreted in combination with other routine clinical factors (p. 1474) and in situations where the results are likely to affect medical management (p. 1475).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer 4.2026
https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

This guideline recommends use of advanced risk stratification tools (i.e., gene expression biomarkers, AI digital pathology) for disease management, most commonly for men with localized prostate cancer and life expectancy of 5-10 years or more (p. PROS-3, 4, 5, and 6). The most common reasons to use these tools are for deciding between active surveillance and radical treatment, predicting long-term outcome, or guiding therapeutic decisions (p. PROS-H 2 and 3 of 6).

These tests should not be used for low-risk disease as they have not been validated in these populations and there are no current treatment implications based on the results (p. PROS-H 3, 4, and 5 of 6). The following tumor-based assays are called out for use: Decipher and ArteraAI Prostate (p. PROS-H 4 and 5 of 6).

Risk stratification testing is recommended for individuals who are post-radical prostatectomy with either PSA persistence or recurrence, who have a life expectancy greater than 5 years (p. PROS-9 and PROS-9A).

Definitions

1. **Algorithmic test** is one that combines biomarkers and clinical data into an algorithm to generate a disease risk assessment, prognostic result, or clinical recommendation for treatment.

Rapid Exome Sequencing

1. Rapid exome sequencing (rES), with trio testing when possible, is considered **medically necessary** when:

    1. The member is an acutely-ill infant (12 months of age or younger), **AND**

    2. The member has not previously had genome sequencing, **AND**

    3. Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection, isolated prematurity), **AND**

    4. Clinical presentation does not fit a well-described syndrome for which rapid single-gene or targeted multi-gene panel testing is available, **AND**

    5. The member's personal and family histories have been evaluated by a Medical Geneticist, Genetic Counselor or an Advanced Practice Nurse in Genetics (APGN), **AND**

    6. The member meets at least one of the following criteria:

        1. The member has unexplained epilepsy, **OR**

        2. The member has global developmental delay, **OR**

        3. The member was diagnosed with at least one congenital anomaly (functional and/or structural), **OR**

        4. The member has at least **TWO** of the following:

            1) Bilateral sensorineural hearing loss of unknown etiology, **OR**

2) Symptoms of a complex neurological disorder (e.g., dystonia, hemiplegia, spasticity, myopathy, muscular dystrophy), **OR**

3) Family history suggestive of a genetic etiology, including consanguinity, **OR**

4) Clinical or laboratory findings suggestive of an inborn error of metabolism, **OR**

5) Severe neuropsychiatric condition (e.g., schizophrenia, bipolar disorder, Tourette syndrome, self-injurious behavior, reverse sleep-wake cycles), **OR**

6) Findings suggestive of inborn error of immunity, **OR**

7) Period of unexplained developmental regression (unrelated to epilepsy or autism).

2. Rapid exome sequencing (rES) is considered **investigational** for all other indications, including screening asymptomatic/healthy individuals for genetic disorders.

Rationale and References

Seattle Children's Hospital Patient-centered Laboratory Utilization Guidance Services. Exome and Genome Sequencing for Rare Disease. Effective June 2025.
https://www.schplugs.org/wp-content/uploads/Exome-and-Genome-Sequencing-for-Rare-Disease.pdf

PLUGS released a guideline entitled “Exome and Genome Sequencing for Rare Disease” in June of 2025, replacing their 2023 guideline entitled “Genomic Sequencing for Rare Disease.” This guideline affirmed the medical necessity of exome sequencing when no targeted testing is

available for the clinical presentation, the etiology is unknown following clinical and radiological evaluation, and one of the following is true (p.1): Specific features including epilepsy, bilateral sensorineural hearing loss, moderate to severe intellectual disability, global developmental delay, multiple congenital anomalies, or inborn errors of immunity are present OR A combination of personal and family history features including neuropsychiatric, metabolic, unexplained developmental regression, and single organ system abnormalities are present

The guideline also includes a recommendation to rule out alternate etiologies prior to testing, when possible.

***National Society of Genetic Counselors. Secondary and Incidental Findings in Genetic Testing. Released September 27, 2013. Updated March 23, 2020. Reaffirmed 2023. https://www.nsgc.org/Policy-Research-and-Publications/Position-Statements/Position-Statements/Post/secondary-and-incidental-findings-in-genetic-testing-1 ***

The National Society for Genetic Counselors (NSGC) released a position statement (2013, updated 2020, reaffirmed 2023) stating the following in regard to secondary and incidental findings in genetic testing: The National Society of Genetic Counselors strongly advises pre-test counseling that facilitates informed decision-making, elicits patient preferences regarding secondary and/or incidental findings if possible, and formulates a plan for returning such results before testing occurs.

Heimall JR, Hagin D, Hajjar J, et al. Use of Genetic Testing for Primary Immunodeficiency Patients. J Clin Immunol. 2018;38(3):320-329. doi:10.1007/s10875-018-0489-8

In a 2017 statement, the Clinical Immunological Society supports the use of genetic testing in individuals with a primary immunodeficiency. They make no recommendation for a specific tiered approach in this population, but support testing that is cost-effective, timely, and likely to result in a diagnosis. Depending on an individual's clinical presentation, they discuss that a whole genomic approach may be appropriate.

Kingsmore SF, Cakici JA, Clark MM, et al. A Randomized, Controlled Trial of the Analytic and Diagnostic Performance of Singleton and Trio, Rapid Genome and Exome Sequencing in Ill Infants. Am J Hum Genet. 2019;105(4):719-733. doi:10.1016/j.ajhg.2019.08.009

The NSIGHT2 study, a prospective randomized, controlled, blinded trial (RCT) in acutely ill infants, found that 24% of infants undergoing rapid exome sequencing had genetic disease. They conclude that diagnostic testing in infants with diseases of unknown etiology, rapid genomic sequencing, including rapid exome sequencing can be performed as a first tier test in infants with diseases of unknown etiology at time of admission to ICUs. In unstable infants and in those whom a genetic diagnosis was likely to impact immediate management, rapid genomic sequencing had optimal analytic and diagnostic performance by virtue of shortest time to results (p. 725).

Li MM, Tayoun AA, DiStefano M, et al. Clinical evaluation and etiologic diagnosis of hearing loss: A clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2022;24(7):1392-1406. doi:10.1016/j.gim.2022.03.018

In 2022, ACMG released a clinical practice resource for the clinical evaluation of hearing loss, which states that first-line genetic testing for individuals with exam findings that suggest a syndromic hearing loss etiology may include a variety of tests, including genome sequencing, depending on clinical presentation. For individuals without physical findings that suggest a syndromic hearing loss etiology, they recommend a tiered approach, starting with comprehensive hearing loss gene panel testing unless a more specific genetic etiology is evident for which targeted testing is appropriate (p. 1400).

Malinowski J, Miller DT, Demmer L, et al. Systematic evidence-based review: outcomes from exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability. Genet Med. 2020;22(6):986-1004. doi:10.1038/s41436-020-0771-z

In 2020, ACMG released a systematic evidence-based review, which “provide[d] indirect evidence of the clinical and personal utility of ES/GS for patients with CA/DD/ID and their family

members", noting that a "change in clinical management" resulted in over half of the patients examined as a result of their ES/GS results (p. 1001).

Manickam K, McClain MR, Demmer LA, et al. Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: an evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23(11):2029-2037. doi:10.1038/s41436-021-01242-6

In 2021, ACMG published an evidence-based clinical practice guideline on exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability), which included the following: "We strongly recommend ES and GS as a first- or second-tier test… for patients with one or more congenital anomalies prior to one year of age, or for patients with intellectual disability/developmental delay with onset prior to 18 years of age (p. 2031). "Isolated autism without ID or congenital malformation is formally out of scope for this recommendation but evaluation of exome/genome studies is ongoing" (p. 2034).

Bélanger SA, Caron J. Evaluation of the child with global developmental delay and intellectual disability. Paediatr Child Health. 2018;23(6):403-419. doi:10.1093/pch/pxy093

A review of the evaluation of children with global developmental delay and intellectual disability by Belanger, et al. (2018) defines global developmental delay (GDD) as the following: Significant delay (at least 2 standard deviations below the mean) in at least two developmental domains (gross or fine motor, speech/language, cognition, social/personal or activities of daily living (p. 404).

Rehm HL, Alaimo JT, Aradhya S, et al. The landscape of reported VUS in multi-gene panel and genomic testing: Time for a change. Genet Med. 2023 Dec;25(12):100947. Epub 2023 Jul 30. doi:10.1016/j.gim.2023.100947.

A 2023 paper by Rehm, et al. demonstrated that exome and genome sequencing had a significantly lower VUS rate (22.5%) compared to multigene panels (32.6%) (p. 5 and 6).

Smith L, Malinowski J, Ceulemans S, et al. Genetic testing and counseling for the unexplained epilepsies: An evidence-based practice guideline of the National Society of Genetic Counselors. J Genet Couns. 2023;32(2):266-280. doi:10.1002/jgc4.1646

The National Society of Genetic Counselors (NSGC) published evidence-based practice guidelines for individuals with unexplained epilepsy (2022). The NSGC recommendations are as follows (p. 4): Individuals with unexplained epilepsy should be offered genetic testing, without limitation of age. Multi-gene, comprehensive testing, such as exome sequencing, genome sequencing or a multigene panel as a first-tier test is strongly recommended.

Definitions

1. **Advanced** cancer (advanced stages or advanced tumor or advanced/metastatic): Cancer that is unlikely to be cured or controlled with treatment. The cancer may have spread from where it first started to nearby tissue, lymph nodes, or distant parts of the body. Treatment may be given to help shrink the tumor, slow the growth of cancer cells, or relieve symptoms.
2. **Advanced** cancer (advanced stages or advanced tumor or advanced/metastatic) is unlikely to be cured or controlled with treatment. The cancer may have spread from where it first started to nearby tissue, lymph nodes, or distant parts of the body. Treatment may be given to help shrink the tumor, slow the growth of cancer cells, or relieve symptoms.
3. **Developmental delay** (DD) is defined as slow-to-meet or not reaching milestones in one or more of the areas of development (communication, motor, cognition, social-emotional, or adaptive skills) in the expected way for a child's age.
4. **Exome Sequencing (ES)** is a genomic technique for sequencing all of the protein-coding regions of genes in the genome (also known as the exome).
5. **Genome Sequencing (GS)** is a genomic technique for sequencing the complete DNA sequence, which includes protein coding as well as non-coding DNA elements.

6. **Global Developmental delay** is diagnosed when a child under age 5 is slow-to-meet or not reaching milestones in the expected way for their age in at least two areas of development (communication, gross/fine motor, cognition, social-emotional, or adaptive skills). Examples include (but are not limited to): not sitting independently by 9 months; not crawling or rolling over by a year; not walking by 18 months (based on CDC Developmental milestones)**.**
7. **Trio Testing** is testing of the child and both biological/genetic parents, which increases the chances of finding a definitive diagnosis while reducing false-positive findings.

Rapid Genome Sequencing

1. Rapid genome sequencing (rGS), with trio testing when possible, is considered **medically necessary** when:

    1. The member is an acutely-ill infant (12 months of age or younger), **AND**

    2. Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection, isolated prematurity), **AND**

    3. Clinical presentation does not fit a well-described syndrome for which rapid single-gene or targeted multi-gene panel testing is available, **AND**

    4. The member's personal and family histories have been evaluated by a Medical Geneticist, Genetic Counselor or an Advanced Practice Nurse in Genetics (APGN), **AND**

    5. The member meets at least one of the following clinical findings:

        1. The member has unexplained epilepsy, **OR**

        2. The member has multiple congenital anomalies (functional and/or structural) affecting unrelated organ systems, **OR**

        3. The member has epileptic encephalopathy, **OR**

        4. The member has at least **TWO** of the following:

            1) Abnormality affecting at least one organ system, **OR**

2) Symptoms of a complex neurological condition (e.g., dystonia, hemiplegia, spasticity, epilepsy, hypotonia, myopathy, muscular dystrophy, global developmental delay, intellectual disability), **OR**

3) Family history suggestive of a genetic etiology, including consanguinity, **OR**

4) Laboratory findings suggestive of an inborn error of metabolism, **OR**

5) Abnormal response to standard therapy.

2. Rapid genome sequencing (rGS) is considered **investigational** for all other indications, including screening asymptomatic/healthy individuals for genetic disorders.

NOTE: When genome sequencing is performed, the mitochondrial genome is assumed to be included as a part of the analysis.

Rationale and References

***Seattle Children's Hospital Patient-centered Laboratory Utilization Guidance Services. Rapid Genome Sequencing. Effective June 2022.https://www.schplugs.org/wp-content/uploads/Rapid-Genome-Sequencing-Policy_June-2022-FINAL.pdf ***

PLUGS released a guideline entitled “Rapid Genome Sequencing” in June of 2022. The authors specify that rapid genome sequencing (rGS) should be used only when (it) “is more efficient and economical than the separate single-gene tests or panels that would be recommended based on the differential diagnosis…” (p. 3 and 4).

This guideline affirmed the medical necessity of exome sequencing in “acutely-ill individuals” when their phenotype has an unknown, likely genetic etiology and one of the following is true:

The patient has multiple multisystemic congenital anomalies or epileptic encephalopathy. A combination of personal and family history features including complex neurological conditions, single organ system or metabolic abnormalities, failure of standard treatment, or consanguinity present. Alternate etiologies have been considered and ruled out when possible (e.g., MRI abnormalities/brain malformations, environmental exposure, injury, infection, isolated prematurity).

Rehm HL, Alaimo JT, Aradhya S, et al. The landscape of reported VUS in multi-gene panel and genomic testing: Time for a change. Genet Med. 2023 Dec;25(12):100947. Epub 2023 Jul 30. doi:10.1016/j.gim.2023.100947.

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The NSIGHT2 study, a prospective randomized, controlled, blinded trial (RCT) in acutely ill infants, primarily from the NICU, PICU, and CVICU at Rady Children's Hospital, San Diego (RCHSD), compared the effectiveness and outcomes between rWGS and rWES, with analysis as singleton probands and familial trios. The inclusion criteria for the 1,248 ill infants defined the maximum age at the time of admission as four months. They found that 24% of infants undergoing rapid exome sequencing had genetic disease. They conclude that diagnostic testing in infants with diseases of unknown etiology, rapid genomic sequencing, including rapid exome sequencing can be performed as a first tier test in infants with diseases of unknown etiology at time of admission to ICUs. In unstable infants and in those whom a genetic diagnosis was likely to impact immediate management, rapid genomic sequencing had optimal analytic and diagnostic performance by virtue of shortest time to results (p. 725).

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Secondary and Incidental Findings in Genetic Testing. Position Statement from National Society of Genetic Counselors. https://www.nsgc.org/Policy-Research-and-Publications/Position-Statements/Position-Statements/Post/secondary-and-incidental-findings-in-genetic-testing-1. Released September 27, 2013. Updated March 23, 2020. Reaffirmed 2023.

The National Society for Genetic Counselors (NSGC) released a position statement (2013, updated 2020, reaffirmed 2023) stating the following in regard to secondary and incidental findings in genetic testing: The National Society of Genetic Counselors strongly advises pre-test counseling that facilitates informed decision-making, elicits patient preferences regarding secondary and/or incidental findings if possible, and formulates a plan for returning such results before testing occurs.

Definitions

1. **Advanced** cancer (advanced stages or advanced tumor or advanced/metastatic): Cancer that is unlikely to be cured or controlled with treatment. The cancer may have spread from where it first started to nearby tissue, lymph nodes, or distant parts of the body. Treatment may be given to help shrink the tumor, slow the growth of cancer cells, or relieve symptoms.

2. **Advanced** cancer (advanced stages or advanced tumor or advanced/metastatic) is unlikely to be cured or controlled with treatment. The cancer may have spread from where it first started to nearby tissue, lymph nodes, or distant parts of the body. Treatment may be given to help shrink the tumor, slow the growth of cancer cells, or relieve symptoms.
3. **Congenital anomalies** (according to ACMG) are anomalies not specific to a well-delineated genetic syndrome. These are structural or functional abnormalities requiring medical intervention that are usually evident at birth, or shortly thereafter, and are consequential to an individual's life expectancy, health status, or physical/social functioning.
4. **Developmental delay** (DD) is defined as slow-to-meet or not reaching milestones in one or more of the areas of development (communication, motor, cognition, social-emotional, or adaptive skills) in the expected way for a child's age.
5. **Genome Sequencing (GS)** is a genomic technique for sequencing the complete DNA sequence, which includes protein coding as well as non-coding DNA elements.
6. **Global Developmental delay** is diagnosed when a child under age 5 is slow-to-meet or not reaching milestones in the expected way for their age in at least two areas of development (communication, gross/fine motor, cognition, social-emotional, or adaptive skills). Examples include (but are not limited to): not sitting independently by 9 months; not crawling or rolling over by a year; not walking by 18 months (based on CDC Developmental milestones)**.**
7. **Intellectual disability (ID)** is defined by the DSM V as an individual age 5 or older with either an IQ score of 70 or below, OR with a clinical diagnosis of intellectual disability per the DSM V, which includes all of the following:
    1. Deficits in intellectual functions, such as reasoning, problem solving, planning, abstract thinking, judgment, academic learning, and learning from experience, confirmed by both clinical assessment and individualized, standardized intelligence testing.
    2. Deficits in adaptive functioning that result in failure to meet developmental and sociocultural standards for personal independence and social responsibility. Without ongoing support, the adaptive deficits limit functioning in one or more

activities of daily life, such as communication, social participation, and independent living, across multiple environments, such as home, school, work, and community.

3. Onset of intellectual and adaptive deficits during the developmental period.

8. **Multiple congenital anomalies,** according to ACMG, are not specific to a well-delineated genetic syndrome. These anomalies are structural or functional abnormalities usually evident at birth, or shortly thereafter, and can be consequential to an individual's life expectancy, health status, physical or social functioning, and typically require medical intervention.
9. **Trio Testing** is testing of the child and both biological/genetic parents, which increases the chances of finding a definitive diagnosis while reducing false-positive findings.

Reanalysis of Exome or Genome Sequencing Data

1. Reanalysis of exome or genome sequencing data is considered **medically necessary** when[1]:

    1. The member had exome sequencing or genome sequencing at least 1 year ago, **OR**

    2. The member's phenotype has expanded to include clinical findings[2] that were not present at the time of the initial exome sequencing or genome sequencing analysis, **AND**

        1. Results of prior exome sequencing or genome sequencing do not explain these new clinical findings.

2. Reanalysis of exome or genome sequencing data is considered **investigational** for all other indications.

[1] If reanalysis of exome data is not possible, see the genome sequencing criteria for additional coverage information.

[2] See [Standard Exome Sequencing](https://app.concertgenetics.com/apps/policies/#/policy/05008_SP_MULTI#EXOME_SEQ) or [Standard Genome Sequencing](https://app.concertgenetics.com/apps/policies/#/policy/05008_SP_MULTI#STAND_GENOME) criteria for qualifying clinical findings.

Rationale and References

Deignan JL, Chung WK, Kearney HM, et al. Points to consider in the reevaluation and reanalysis of genomic test results: a statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2019;21(6):1267-1270. doi:10.1038/s41436-019-0478-1

A statement from ACMG (2019, reaffirmed 2023) included considerations for case-level exome reanalysis, which include the following: Significant improvements have been made to bioinformatics handling of the data (alignment/variant calling and/or the automated filtering

processes) Updated clinical and family history information, which may result in the identification of additional variants that are associated with the indication(s) for testing (p. 1269).

Rodan LH, Stoler J, Chen E, Geleske T; Council on Genetics. Genetic evaluation of the child with intellectual disability or global developmental delay: clinical report. Pediatrics. 2025;156(1):e2025072219. doi:10.1542/peds.2025-072219

This 2025 AAP report provided general guidance regarding genetic testing recommendations for individuals with global developmental delay (GDD) or intellectual disability (ID). The AAP took into consideration the diagnostic yield, cost of testing, and test complexity (p. 4) and proposed a "tiered agnostic approach" to diagnostic evaluation of GDD/ID (p. 5). In this approach, the Tier 1 testing includes exome or genome sequencing; Tier 2 testing includes Fragile X and inborn errors of metabolism, and Tier 3 includes genome sequencing (if not already performed), as well as additional more specialized tests. They state that if Tier 3 testing is negative/uninformative, then exome or genome sequencing could be reanalyzed every 1-2 years following the initial test (p. 7).

Alfares A, Aloraini T, Subaie LA, et al. Whole-genome sequencing offers additional but limited clinical utility compared with reanalysis of whole-exome sequencing. Genet Med. 2018;20(11):1328-1333. doi:10.1038/gim.2018.41

This study from 2018 compared the detection rates of whole exome sequencing (WES) and whole genome sequencing (WGS) in a clinical setting. The study included 108 patients with negative array CGH and negative or inconclusive WES results. WGS was performed on all patients, and the results of the study showed that 30% of the positive cases identified by WGS could be identified by reanalyzing WES raw data, and WGS achieved an only 7% higher detection rate (p. 1328). The paper concluded that, although WGS is a more powerful tool than WES, in this study, "we showed that WGS has additional, but limited, clinical utility compared with reanalyzing WES data, and until the cost of WGS approximates that of WES, reanalyzing WES raw data is recommended before performing WGS" (p. 1333).

Reddi HV, Avenarius MR, Bean LJH, et al. Addendum: Points to consider in the reevaluation and reanalysis of genomic test results: A statement of the American College of Medical Genetics and Genomics (ACMG). Genetics in Medicine. 2024;26(5):101100. doi:10.1016/j.gim.2024.101100

A statement from ACMG (2019, reaffirmed 2023) included considerations for case-level exome reanalysis, which include the following: Significant improvements have been made to bioinformatics handling of the data (alignment/variant calling and/or the automated filtering processes) Updated clinical and family history information, which may result in the identification of additional variants that are associated with the indication(s) for testing (p. 1269).

Seattle Children's Hospital Patient-centered Laboratory Utilization Guidance Services. Exome and Genome Sequencing for Rare Disease. Effective June 2025. https://www.schplugs.org/wp-content/uploads/Exome-and-Genome-Sequencing-for-Rare-Disease.pdf

The PLUGS guideline entitled “Exome and Genome Sequencing for Rare Disease” (2025) state the following regarding reanalysis of exome or genome sequencing data: Periodic reanalysis of previously obtained exome or genome sequence has the potential for additional diagnostic yield because of expanding variant databases, as well as periodic novel gene discovery and publication. A review of twenty-seven peer-reviewed articles revealed a median new diagnosis rate via reanalysis of 15% and median reanalysis timeframe of 22 months. The authors suggest that an interval of greater than 18 months from the original report may be optimal for reanalysis (p. 4).

The guideline also states: Re-analysis of previously obtained exome or genome sequence has the potential for additional diagnostic yield because of expanding variant databases, as well as periodic novel gene discovery and publication. Re-analysis could be considered prior to additional genomic sequencing, particularly if there has been onset or identification of additional symptoms that broadens the clinical phenotype assessed during the original ES/GS analysis… (p. 2).

Definitions

1. **Exome Sequencing (ES)** is a genomic technique for sequencing all of the protein-coding regions of genes in the genome (also known as the exome).
2. **Genome Sequencing (GS)** is a genomic technique for sequencing the complete DNA sequence, which includes protein coding as well as non-coding DNA elements.

Standard Exome Sequencing

1. Standard exome sequencing, with trio testing when possible, is considered **medically necessary** when:

    1. The member has not previously had genome sequencing, **AND**

    2. Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection, isolated prematurity), **AND**

    3. Clinical presentation does not fit a well-described syndrome for which single-gene or targeted multigene panel testing is available, **AND**

    4. The member's personal and family histories have been evaluated by a Medical Geneticist, Genetic Counselor or an Advanced Practice Nurse in Genetics (APGN), **AND**

    5. The member meets at least one of the following clinical findings:

        1. The member has unexplained epilepsy diagnosed at any age, **OR**

        2. The member has global developmental delay or intellectual disability with onset prior to age 18 years, **OR**

        3. The member was diagnosed with at least one congenital anomaly (functional and/or structural), **OR**

        4. The member has at least **TWO** of the following:

            1) Bilateral sensorineural hearing loss of unknown etiology, **OR**

2) Symptoms of a complex neurological disorder (e.g., dystonia, hemiplegia, spasticity, epilepsy, myopathy, muscular dystrophy), **OR**

3) Family history suggestive of a genetic etiology, including consanguinity, **OR**

4) Clinical or laboratory findings suggestive of an inborn error of metabolism, **OR**

5) Autism spectrum disorder, **OR**

6) Severe neuropsychiatric condition (e.g., schizophrenia, bipolar disorder, Tourette syndrome, self-injurious behavior, reverse sleep-wake cycles), **OR**

7) Findings suggestive of inborn error of immunity, **OR**

8) Period of unexplained developmental regression (unrelated to epilepsy or autism).

2. Repeat standard exome sequencing is considered **investigational**.

3. Standard exome sequencing is considered **investigational** for all other indications, including screening asymptomatic/healthy individuals for genetic disorders.

Rationale and References

Bélanger SA, Caron J. Evaluation of the child with global developmental delay and intellectual disability. Paediatr Child Health. 2018;23(6):403-419. doi:10.1093/pch/pxy093

A review of the evaluation of children with global developmental delay and intellectual disability by Belanger, et al. (2018) defines global developmental delay (GDD) as the following: Significant delay (at least 2 standard deviations below the mean) in at least two developmental domains (gross or fine motor, speech/language, cognition, social/personal or activities of daily living (p. 404). This diagnosis is reserved for children under age 5.

Heimall JR, Hagin D, Hajjar J, et al. Use of Genetic Testing for Primary Immunodeficiency Patients. J Clin Immunol. 2018;38(3):320-329. doi:10.1007/s10875-018-0489-8

In a 2017 statement, the Clinical Immunological Society supports the use of genetic testing in individuals with a primary immunodeficiency. They make no recommendation for a specific tiered approach in this population, but support testing that is cost-effective, timely, and likely to result in a diagnosis. Depending on an individual's clinical presentation, they discuss that a whole genomic approach may be appropriate.

Smith L, Malinowski J, Ceulemans S, et al. Genetic testing and counseling for the unexplained epilepsies: An evidence-based practice guideline of the National Society of Genetic Counselors. J Genet Couns. 2023;32(2):266-280. doi:10.1002/jgc4.1646

The National Society of Genetic Counselors (NSGC) published evidence-based practice guidelines for individuals with unexplained epilepsy (2022). The NSGC recommendations are as follows (p. 4): Individuals with unexplained epilepsy should be offered genetic testing, without limitation of age. Multi-gene, comprehensive testing, such as exome sequencing, genome sequencing or a multigene panel as a first-tier test is strongly recommended.

Rodan LH, Stoler J, Chen E, Geleske T; Council on Genetics. Genetic evaluation of the child with intellectual disability or global developmental delay: clinical report. Pediatrics. 2025;156(1):e2025072219. doi:10.1542/peds.2025-072219

This 2025 AAP report provided general guidance regarding genetic testing recommendations for individuals with global developmental delay (GDD) or intellectual disability (ID). The AAP took into

consideration the diagnostic yield, cost of testing, and test complexity (p. 4) and proposed a "tiered agnostic approach" to diagnostic evaluation of GDD/ID (p. 5). In this approach, the Tier 1 testing includes exome or genome sequencing; Tier 2 testing includes Fragile X and inborn errors of metabolism, and Tier 3 includes genome sequencing (if not already performed), as well as additional more specialized tests.

Manickam K, McClain MR, Demmer LA, et al. Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: an evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23(11):2029-2037. doi:10.1038/s41436-021-01242-6

In 2021, ACMG published an evidence-based clinical practice guideline on exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability, which included the following statements: "We strongly recommend ES and GS as a first- or second-tier test… for patients with one or more congenital anomalies prior to one year of age, or for patients with intellectual disability/developmental delay with onset prior to 18 years of age" (p. 2031) "Isolated autism without ID or congenital malformation is formally out of scope for this recommendation but evaluation of exome/genome studies is ongoing" (p. 2034)

Li MM, Tayoun AA, DiStefano M, et al. Clinical evaluation and etiologic diagnosis of hearing loss: A clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2022;24(7):1392-1406. doi:10.1016/j.gim.2022.03.018

In 2022, ACMG released a clinical practice resource for the clinical evaluation of hearing loss, which states that first-line genetic testing for individuals with exam findings that suggest a syndromic hearing loss etiology may include a variety of tests, including genome sequencing, depending on clinical presentation. For individuals without physical findings that suggest a syndromic hearing loss etiology, they recommend a tiered approach, starting with comprehensive hearing loss gene panel testing unless a more specific genetic etiology is evident for which targeted testing is appropriate (p. 1400).

***National Society of Genetic Counselors. Secondary and Incidental Findings in Genetic Testing. Released September 27, 2013. Updated March 23, 2020. Reaffirmed 2023. https://www.nsgc.org/Policy-Research-and-Publications/Position-Statements/Position-Statements/Post/secondary-and-incidental-findings-in-genetic-testing-1 ***

The National Society for Genetic Counselors (NSGC) released a position statement (2013, updated 2020, reaffirmed 2023) stating the following in regard to secondary and incidental findings in genetic testing: The National Society of Genetic Counselors strongly advises pre-test counseling that facilitates informed decision-making, elicits patient preferences regarding secondary and/or incidental findings if possible, and formulates a plan for returning such results before testing occurs.

Seattle Children's Hospital Patient-centered Laboratory Utilization Guidance Services. Exome and Genome Sequencing for Rare Disease. Effective June 2025. https://www.schplugs.org/wp-content/uploads/Exome-and-Genome-Sequencing-for-Rare-Disease.pdf

PLUGS released a guideline entitled “Exome and Genome Sequencing for Rare Disease” in June of 2025, replacing their 2023 guideline entitled “Genomic Sequencing for Rare Disease.” This guideline affirmed the medical necessity of exome sequencing when no targeted testing is available for the clinical presentation, the etiology is unknown following clinical and radiological evaluation, and one of the following is true (p.1): Specific features including epilepsy, bilateral sensorineural hearing loss, moderate to severe intellectual disability, global developmental delay, multiple congenital anomalies, or inborn errors of immunity are present OR A combination of personal and family history features including neuropsychiatric, metabolic, unexplained developmental regression, and single organ system abnormalities are present

The guideline also includes a recommendation to rule out alternate etiologies prior to testing, when possible.

Definitions

1. **Advanced** cancer (advanced stages or advanced tumor or advanced/metastatic): Cancer that is unlikely to be cured or controlled with treatment. The cancer may have spread from where it first started to nearby tissue, lymph nodes, or distant parts of the body. Treatment may be given to help shrink the tumor, slow the growth of cancer cells, or relieve symptoms.
2. **Advanced** cancer (advanced stages or advanced tumor or advanced/metastatic) is unlikely to be cured or controlled with treatment. The cancer may have spread from where it first started to nearby tissue, lymph nodes, or distant parts of the body. Treatment may be given to help shrink the tumor, slow the growth of cancer cells, or relieve symptoms.
3. **Autism spectrum disorder** is defined in the DSM V as persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history:
   1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.
   2. Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.
   3. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.
4. **Developmental delay** (DD) is defined as slow-to-meet or not reaching milestones in one or more of the areas of development (communication, motor, cognition, social-emotional, or adaptive skills) in the expected way for a child's age.
5. **Exome Sequencing (ES)** is a genomic technique for sequencing all of the protein-coding regions of genes in the genome (also known as the exome).

6. **Genome Sequencing (GS)** is a genomic technique for sequencing the complete DNA sequence, which includes protein coding as well as non-coding DNA elements.
7. **Global Developmental delay** is diagnosed when a child under age 5 is slow-to-meet or not reaching milestones in the expected way for their age in at least two areas of development (communication, gross/fine motor, cognition, social-emotional, or adaptive skills). Examples include (but are not limited to): not sitting independently by 9 months; not crawling or rolling over by a year; not walking by 18 months (based on CDC Developmental milestones)**.**
8. **Intellectual disability (ID)** is defined by the DSM V as an individual age 5 or older with either an IQ score of 70 or below, OR with a clinical diagnosis of intellectual disability per the DSM V, which includes all of the following:
    1. Deficits in intellectual functions, such as reasoning, problem solving, planning, abstract thinking, judgment, academic learning, and learning from experience, confirmed by both clinical assessment and individualized, standardized intelligence testing.
    2. Deficits in adaptive functioning that result in failure to meet developmental and sociocultural standards for personal independence and social responsibility. Without ongoing support, the adaptive deficits limit functioning in one or more activities of daily life, such as communication, social participation, and independent living, across multiple environments, such as home, school, work, and community.
    3. Onset of intellectual and adaptive deficits during the developmental period.
9. **Trio Testing** is testing of the child and both biological/genetic parents, which increases the chances of finding a definitive diagnosis while reducing false-positive findings.

Standard Genome Sequencing

1. Standard genome sequencing, with trio testing when possible, is considered **medically necessary** when:

    1. Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection, isolated prematurity), **AND**

    2. Clinical presentation does not fit a well-described syndrome for which single-gene or targeted multigene panel testing is available, **AND**

    3. The member's personal and family histories have been evaluated by a Medical Geneticist, Genetic Counselor or an Advanced Practice Nurse in Genetics (APGN), **AND**

    4. The member meets at least one of the following clinical findings:

        1. The member has unexplained epilepsy diagnosed at any age, **OR**

        2. The member has global developmental delay or intellectual disability with onset prior to age 18 years, **OR**

        3. The member was diagnosed with at least one congenital anomaly (functional and/or structural), **OR**

        4. The member has at least **TWO** of the following:

            1) Bilateral sensorineural hearing loss of unknown etiology, **OR**

            2) Symptoms of a complex neurological disorder (e.g., dystonia, hemiplegia, spasticity, epilepsy, myopathy, muscular dystrophy), **OR**

3) Family history suggestive of a genetic etiology, including consanguinity, **OR**

4) Clinical or laboratory findings suggestive of an inborn error of metabolism, **OR**

5) Autism spectrum disorder, **OR**

6) Severe neuropsychiatric condition (e.g., schizophrenia, bipolar disorder, Tourette syndrome, self-injurious behavior, reverse sleep-wake cycles), **OR**

7) Findings suggestive of inborn error of immunity, **OR**

8) Period of unexplained developmental regression (unrelated to epilepsy or autism).

2. Repeat standard genome sequencing is considered **investigational**.

3. Standard genome sequencing is considered **investigational** for all other indications, including screening asymptomatic/healthy individuals for genetic disorders.

Note: When genome sequencing is performed, the mitochondrial genome is assumed to be included as a part of the analysis.

Rationale and References

Heimall JR, Hagin D, Hajjar J, et al. Use of Genetic Testing for Primary Immunodeficiency Patients. J Clin Immunol. 2018;38(3):320-329. doi:10.1007/s10875-018-0489-8

In a 2017 statement, the Clinical Immunological Society supports the use of genetic testing in individuals with a primary immunodeficiency. They make no recommendation for a specific tiered

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Rehm HL, Alaimo JT, Aradhya S, et al. The landscape of reported VUS in multi-gene panel and genomic testing: Time for a change. Genet Med. 2023 Dec;25(12):100947. Epub 2023 Jul 30. doi:10.1016/j.gim.2023.100947.

A 2023 paper by Rehm, et al. demonstrated that exome and genome sequencing had a significantly lower VUS rate (22.5%) compared to multigene panels (32.6%) (p. 5 and 6).

Rodan LH, Stoler J, Chen E, Geleske T; Council on Genetics. Genetic evaluation of the child with intellectual disability or global developmental delay: clinical report. Pediatrics. 2025;156(1):e2025072219. doi:10.1542/peds.2025-072219

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***National Society of Genetic Counselors. Secondary and Incidental Findings in Genetic Testing. Released September 27, 2013. Updated March 23, 2020. Reaffirmed 2023. https://www.nsgc.org/Policy-Research-and-Publications/Position-Statements/Position-Statements/Post/secondary-and-incidental-findings-in-genetic-testing-1 ***

The National Society for Genetic Counselors (NSGC) released a position statement (2013, updated 2020, reaffirmed 2023) stating the following in regard to secondary and incidental

findings in genetic testing: The National Society of Genetic Counselors strongly advises pre-test counseling that facilitates informed decision-making, elicits patient preferences regarding secondary and/or incidental findings if possible, and formulates a plan for returning such results before testing occurs.

Definitions

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2. **Advanced** cancer (advanced stages or advanced tumor or advanced/metastatic) is unlikely to be cured or controlled with treatment. The cancer may have spread from where it first started to nearby tissue, lymph nodes, or distant parts of the body. Treatment may be given to help shrink the tumor, slow the growth of cancer cells, or relieve symptoms.
3. **Autism spectrum disorder** is defined in the DSM V as persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history:
   1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.
   2. Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.
   3. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.

4. **Developmental delay** (DD) is defined as slow-to-meet or not reaching milestones in one or more of the areas of development (communication, motor, cognition, social-emotional, or adaptive skills) in the expected way for a child's age.
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7. **Intellectual disability (ID)** is defined by the DSM V as an individual age 5 or older with either an IQ score of 70 or below, OR with a clinical diagnosis of intellectual disability per the DSM V, which includes all of the following:
    1. Deficits in intellectual functions, such as reasoning, problem solving, planning, abstract thinking, judgment, academic learning, and learning from experience, confirmed by both clinical assessment and individualized, standardized intelligence testing.
    2. Deficits in adaptive functioning that result in failure to meet developmental and sociocultural standards for personal independence and social responsibility. Without ongoing support, the adaptive deficits limit functioning in one or more activities of daily life, such as communication, social participation, and independent living, across multiple environments, such as home, school, work, and community.
    3. Onset of intellectual and adaptive deficits during the developmental period.
8. **Trio Testing** is testing of the child and both biological/genetic parents, which increases the chances of finding a definitive diagnosis while reducing false-positive findings.

Thyroid Cancer Diagnostic Algorithmic Tests

1. The use of a thyroid cancer diagnostic algorithmic test in fine needle aspirates of thyroid nodules is considered **medically necessary** when:

    1. The fine needle aspirate showed indeterminate cytologic findings (i.e., Bethesda diagnostic category III or IV), **AND**

    2. The result of the test would affect surgical decision making.

2. The use of a thyroid cancer diagnostic algorithmic test in fine needle aspirates of thyroid nodules is considered **investigational** for all other indications.

Rationale and References

Haugen BR, Alexander EK, Bible KC, et al. American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016;26(1):1-133. doi:10.1089/thy.2015.0020

The ATA developed evidence-based guidelines on the management of thyroid nodules and differentiated thyroid cancer in adults (2016). They state that molecular testing may be used to aid in risk stratification for nodules with AUS/FLUS [atypia of undetermined significance/follicular lesion of undetermined significance] in place of the more traditional strategy of surveillance or diagnostic surgery (p. 21).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Thyroid Carcinoma 1.2025
https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf

This guideline recommends consideration of molecular diagnostics on fine needle aspirate (FNA) results of thyroid nodules which are classified as Bethesda III or Bethesda IV if there is not high clinical and/or radiographic suspicion of malignancy (p. THYR-1 and THYR-2).

Definitions

1. **Algorithmic test** is one that combines biomarkers and clinical data into an algorithm to generate a disease risk assessment, prognostic result, or clinical recommendation for treatment.
2. **Indeterminate cytologic findings** include Bethesda diagnostic category III (atypia/follicular lesion of undetermined significance) or Bethesda diagnostic category IV (follicular neoplasm/suspicion for a follicular neoplasm).

Tumor-Type Agnostic Solid Tumor Molecular Profiling Panels

1. Tumor-type agnostic solid tumor molecular profiling panels are considered **medically necessary** when:

    1. The member meets both of the following:

        1. The member has a diagnosis of:

            1) Recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer, **OR**

            2) Histiocytosis, **OR**

            3) Non-small cell lung cancer (NSCLC) regardless of stage, **OR**

            4) Resectable or borderline resectable pancreatic adenocarcinoma, **OR**

            5) Central nervous system tumor, **OR**

            6) Resectable colon cancer, **AND**

        2. The member is seeking further cancer treatment (e.g., therapeutic chemotherapy), **OR**

    2. The member meets one of the following:

        1. The member is being evaluated for a suspected metastatic malignancy of unknown type, **OR**

        2. The member is undergoing initial evaluation for a known or suspected gastric cancer, **OR**

3. The member has a diagnosis of uterine neoplasm, **AND**

    1) The member is undergoing initial evaluation, **OR**

4. The member is undergoing initial evaluation for a known or suspected gastrointestinal stromal tumor (GIST), **AND**

    1) The tumor is negative for *KIT* and *PDGFRA* mutations.

2. Repeat testing via a tumor-type agnostic solid tumor molecular profiling panel is considered **medically necessary** when:

    1. The member has progression of:

        1. Advanced or metastatic non-small cell lung cancer (NSCLC), **OR**

        2. Advanced or metastatic gastric adenocarcinoma, **OR**

        3. Metastatic prostate cancer, **OR**

        4. Metastatic colorectal cancer.

3. Tumor-type agnostic solid tumor molecular profiling panels are considered **investigational** for all other indications.

NOTE: Additional codes representing additional IHC and/or cytogenetics analyses may be billed alongside the PLA or GSP codes.

Rationale and References

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer 5.2025
https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

This guideline recommends comprehensive somatic testing to aid in clinical management of patients with recurrent/stage IV breast cancer (p. BINV-18).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Pediatric Central Nervous System Cancers 3.2025
https://www.nccn.org/professionals/physician_gls/pdf/ped_cns.pdf

This guideline recommends broad molecular testing to diagnose and classify pediatric diffuse high-grade gliomas (p. PGLIO-B, 2 of 4).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Rectal Cancer 3.2025
https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf

This guideline states that broad molecular testing should be performed for rectal cancer with suspected or proven distant metastases (p. REC-2).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Colon Cancer 4.2025
https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf

This guideline recommends all patients with metastatic colorectal cancer have molecular testing which should be done, if possible, via a broad NGS panel to identify rare and actionable alterations including fusions (p. COL-2, COL-B 4 of 10). Testing can be performed on the primary tumor and/or metastases (p. COL-B 4 of 10). Repeat testing can be considered by clinicians to guide future therapy decisions (p. COL-B 4 of 10).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Occult Primary 2.2025
https://www.nccn.org/professionals/physician_gls/pdf/occult.pdf

This guideline recommends molecular profiling for patients with suspected metastatic epithelial cancer of unknown primary (p. OCC-1, OCC-2).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer 3.2025
https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf

This guideline recommends that patients with recurrent disease undergo comprehensive tumor molecular analysis to identify alterations that would be amenable to targeted therapeutics that have tumor specific or tumor-agnostic benefit (p. OV-6). These guidelines also recommend that molecular testing be performed on the most recent tumor tissue available (p. OV-B, 1 of 3).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma 2.2025
https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf

This guideline recommends tumor/somatic molecular profiling to identify targetable alterations for patients with locally advanced or metastatic disease and recommends consideration of this testing for patients with resectable or borderline resectable disease who are candidates for systemic therapy. Testing can include but is not limited to fusions (ALK, NRG1, NTRK, ROS1, FGFR2, RET), mutations (BRAF, BRCA1/2, KRAS, PALB2), amplifications (HER2), MSI, tumor mutational burden and mismatch repair deficiency (p. PANC-1A, PANC-F, 1 of 13).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Histiocytic Neoplasms 1.2025
https://www.nccn.org/professionals/physician_gls/pdf/histiocytic_neoplasms.pdf

This guideline recommends molecular mutation profiling in the work-up/evaluation of Langerhans Cell Histiocytosis (LCH), Erdheim-Chester Disease (ECD) and Rosai-Dorfman Disease (RDD) for prognostic and treatment information (p. HIST-C, 1 of 5).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Uterine Neoplasms 3.2025
https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf

This guideline recommends comprehensive molecular profiling in the initial evaluation of uterine neoplasms, including uterine sarcoma (p. UTSARC-A1 of 8). This can be done on the initial biopsy or the hysterectomy specimen (p. ENDO-A 2 of 4).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ampullary Adenocarcinoma 2.2025
https://www.nccn.org/professionals/physician_gls/pdf/ampullary.pdf

This guideline recommends somatic molecular profiling to identify uncommon and potentially actionable mutations including fusions, amplifications, MSI, dMMR, and TMB for patients with locally advanced or metastatic disease who are candidates for systemic therapy (p. AMP-6).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Gastrointestinal Stromal Tumors (GIST) 1.2025
https://www.nccn.org/professionals/physician_gls/pdf/gist.pdf

This guideline recommends molecular testing for a suspected or confirmed gastrointestinal stromal tumor when systemic therapy is being considered (p. GIST-1). If testing does not show a KIT or PDGFRA mutation, NGS testing is recommended to look for alternative driver mutations that will identify targeted therapy options (p. GIST-B).

U.S. Food and Drug Administration. FoundationOne CDx: device labeling. PMA No. P170019. Published November 30, 2017.
https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019C.pdf

The FoundationOne CDx test has been approved by the FDA as a companion diagnostic test for several therapies, including some that are indicated for early stage non-small cell lung cancer diagnoses.

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer 8.2025
https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

This guideline has several recommendations regarding biomarker testing:

- Broad molecular profiling is recommended to be performed for stage IV/advanced or metastatic adenocarcinoma, large cell, or NSCLC not otherwise specified. NCCN also recommends consideration of broad molecular profiling for advanced or metastatic squamous cell carcinoma of the lung (p. NSCL-14, NSCL-15, NSCL-19).
- Repeat somatic genetic testing can be helpful to aid in deciding next therapeutic steps when a patient's tumor shows evidence of progression on targeted therapy. Broad genomic profiling may be the best testing method to ensure all possible therapeutic biomarkers are analyzed (p. NSCL-H, 7 of 8).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Gastric Cancer 3.2025
https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf

This guideline recommends consideration of broad NGS testing in place of, or following, sequential testing for individual biomarkers if there is limited tissue available, or late in the course of treatment for numerous targets (p. GAST-B, 6 of 7). The guideline also recommends that repeat tumor testing be considered when there is clinical or radiologic evidence of disease progression in advanced gastric cancer (p. GAST-B, 3 of 7).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer 2.2026
https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

This guideline recommends consideration of somatic multigene tumor testing to identify alterations in HRR genes, in addition to MSI and TMB testing, for patients with metastatic prostate cancer. NCCN recommends consideration of this testing in patients with regional prostate cancer. This guideline also recommends that repeat tumor profiles can be considered at the time of progression of disease (p. PROS-C, 2 of 2).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Central Nervous System Cancers 2.2025
https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf

This guideline recommends next-generation sequencing in the pathologic workup of CNS tumors, since there are now multiple prognostic and diagnostic biomarkers that should be tested to aid in treatment decisions (p. BRAIN-E, 2 of 9).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Small Cell Lung Cancer 2.2026
https://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf

This guideline recommends consideration of comprehensive molecular profiling for extensive stage and relapsed small cell lung cancer (p. SCL-B, 1 of 2), which is defined as stage IV cancer and stage III cancer with extensive local lung nodules or nodal volume (ST-1).

Definitions

1. **Advanced** cancer (advanced stages or advanced tumor or advanced/metastatic): Cancer that is unlikely to be cured or controlled with treatment. The cancer may have spread from where it first started to nearby tissue, lymph nodes, or distant parts of the body. Treatment may be given to help shrink the tumor, slow the growth of cancer cells, or relieve symptoms.
2. **Advanced** cancer (advanced stages or advanced tumor or advanced/metastatic) is unlikely to be cured or controlled with treatment. The cancer may have spread from

where it first started to nearby tissue, lymph nodes, or distant parts of the body. Treatment may be given to help shrink the tumor, slow the growth of cancer cells, or relieve symptoms.

Uveal Melanoma Prognostic Algorithmic Tests

1. The use of a uveal melanoma prognostic algorithmic test is considered **medically necessary** when:

    1. The member has primary, localized uveal melanoma.

2. The use of a uveal melanoma prognostic algorithmic test is considered **investigational** for all other indications.

Rationale and References

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Melanoma: Uveal 1.2025
https://www.nccn.org/professionals/physician_gls/pdf/uveal.pdf

This guideline recommends consideration of biopsy of the primary tumor before radiation for prognostic analysis. Molecular testing for prognostication is recommended over cytology alone (p. UM-2A). Tumor class defined by gene expression profiling was more strongly associated with risk of metastasis than any other prognostic factor (p. UM-4).

Definitions

1. **Algorithmic test** is one that combines biomarkers and clinical data into an algorithm to generate a disease risk assessment, prognostic result, or clinical recommendation for treatment.