Test Specific Guidelines

Chromosomal Microarray for Solid Tumors

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Introduction

Chromosomal microarray analysis of solid tumors is addressed by this guideline.

Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedures addressed by this guideline	Procedure code(s)
Cytogenomic neoplasia microarray analysis	81277

What Are Chromosome Abnormalities in Cancer?

Introduction

Chromosomal aberrations are known to contribute to tumorigenesis.[1]

Chromosome Abnormalities in Cancer

A chromosome abnormality is any difference in the structure, arrangement, or amount of genetic material packaged into the chromosomes. Chromosome abnormalities have been identified in many types of cancer, including leukemias, lymphomas, and solid tumors. Chromosome abnormalities can include deletions, duplications, balanced or unbalanced rearrangements, and gain or loss of whole or partial chromosomes. These abnormalities can play a key role in the development, diagnosis, and monitoring of cancer. The cytogenetics of a cancer can also change over time or in response to treatment. Therefore, chromosome analysis can be used to monitor disease progression and treatment response.

"[C]ancer is thought to be a consequence of genomic alteration accumulation, such as single-nucleotide variants (SNVs) and copy number variants (CNVs), and

structural rearrangements, which encompass deletions, duplications, inversions, insertions, and translocations that could lead to novel fusion genes." [2]

Some chromosome abnormalities are characteristic of certain types of malignancy, and can be used to classify a type or subtype of cancer. For example, codeletion of 1p and 19q along with IDH1/2 mutations indicate oligodendroglioma.[3]

"The presence of specific chromosomal and genetic alterations exclusively observed in malignant cells helps in cancer diagnosis and prognosis, allowing also to quantify residual disease. Several different types and sizes of chromosomal abnormalities can be found in human cancers, being the products of these dysregulated genes and cellular pathways specific targets for new drugs." [2]

Test Information

Introduction

Chromosome analysis of solid tumors can be done through traditional cytogenetic testing (karyotype), fluorescence in situ hybridization (FISH), or chromosomal microarray. This guideline addresses only chromosomal microarray on solid tumors.

Chromosomal Microarray

CMA testing generally works by fluorescently tagging DNA from an individual's test sample with one color and combining it with a control sample tagged in a different color. The two samples are mixed and then added to the array chip, where they compete to hybridize with the DNA fragments on the chip. By comparing the test sample versus the control, computer analysis can determine where genetic material has been deleted or duplicated in the individual.

There are a growing number of CMA testing platforms, including non-chip based applications, which differ in approach and resolution. Clinical laboratories may not only differ in the arrays that they utilize but also in their reporting practices. Although testing guidelines do not endorse one CMA over another, it is typically advisable that coverage of an ordered CMA is better than that offered by a standard karyotype and that the minimum resolution of the CMA provided by the laboratory is adequate. The inclusion of analysis of subtelomeric regions and known microdeletion syndromes with CMA testing obviates the need for additional FISH analysis.

CMA testing offers advantages over conventional karyotyping with regard to resolution and yield. However, there are some limitations of CMA testing including:

- the inability to detect
  - balanced chromosomal rearrangements such as translocations or inversions
  - certain forms of polyploidy
  - sex chromosome aneuploidy dependent on the gender control used
  - low level mosaicism
  - some marker chromosomes
- the detection of CNVs of uncertain clinical significance
- the inability to differentiate free trisomies from unbalanced Robertsonian translocations.

Guidelines and Evidence

Introduction

This section includes relevant guidelines and evidence pertaining to chromosomal microarray in solid tumors.

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG, 2019) provided technical standards and guidelines for interpretation and reporting of acquired copy number abnormalities and loss of heterozygosity in neoplastic disorders:[4]

- "Genomic testing of hematologic malignancies and solid tumors at the time of disease presentation provides information that is crucial for diagnosis and management. This evaluation may include G-banded chromosome analysis, fluorescence in situ hybridization (FISH) analysis, chromosomal microarray analysis (CMA), gene expression and fusion studies, targeted gene sequencing, as well as gene sequencing panels."
- "[A] unified approach for the clinical interpretation, classification, and reporting of all somatic variants will become a necessity."
- Tier 1 variants are those with a strong clinical significance, and several cytogenetic abnormalities in CNS cancers are classified as Tier 1. Additionally, select cytogenetic abnormalities are classified as Tier 1 in the following cancers:
  - Renal cell carcinoma
  - Pediatric embryonal cancers
  - Breast cancer

- Bone cancer
- Gastrointestinal stromal tumors
- Mesothelioma

- "The laboratory must ensure that the clinical report accurately describes the findings and clearly communicates their clinical significance."

The American College of Medical Genetics and Genomics (ACMG, 2016) provided technical standards and guidelines for chromosome analysis in solid tumor-acquired chromosome abnormalities:[5]

- "Genetic analysis of solid tumors and lymphomas at diagnosis provides information critical for diagnosis and patient management."
- "Analysis of tumor tissues may be accomplished by conventional chromosome analysis, fluorescence in situ hybridization (FISH) analysis, chromosomal microarray (CMA) analysis, molecular analysis, or a combination of methodologies."
- "The method(s) chosen for evaluation of a tumor at the time of biopsy or resection will depend on the differential diagnosis, clinical indications, available tissue, available methodologies, and initial histopathology of the tumor tissue."
- "CMA can provide valuable information to supplement that of chromosomal and FISH analyses. Isolated tumor DNA hybridized to whole-genome copy number and/or single nucleotide polymorphism microarrays allows detection of loss, gain, and amplification of regions of DNA, which may not otherwise be detected."
- "[T]umor materials should be studied with available methods to gain as much information as possible at the time of initial study. At a time of suspected disease recurrence or metastasis, the initial genetic data will be used to confirm recurrence or metastasis, assess clonal disease evolution, or reveal a new malignant process."

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2021) guideline on soft tissue sarcoma stated:[6]

- "Morphologic diagnosis based on microscopic examination of histologic sections remains the gold standard for sarcoma diagnosis. However, several ancillary techniques are useful in support of morphologic diagnosis, including IHC, classical cytogenetics, electron microscopy, and molecular genetic testing. Molecular genetic testing has emerged as an ancillary testing approach since many sarcoma types harbor characteristic gene aberrations,

including single base pair substitutions, deletions and amplifications, and translocations. Most molecular testing utilizes fluorescence in situ hybridization (FISH) approaches or polymerase chain reaction (PCR)-based methods and next-generation sequencing (NGS)-based methods."

The National Comprehensive Cancer Network (NCCN, 2021) guideline on central nervous system cancers stated:[7]

- "With the use of genetic and molecular testing, histologically similar CNS neoplasms can be differentiated more accurately in terms of prognosis and, in some instances, response to different therapies."
- "Molecular characterization of primary CNS tumors has substantially impacted clinical trial eligibility and risk stratification in the past 10 years, thereby evolving the standard of care towards an integrated tumor diagnosis in neuro-oncology".
- "Molecular/genetic characterization does not replace standard histologic assessment, but serves as a complementary approach to provide additional diagnostic and prognostic information that often enhances treatment selection."
- "Some diffusely infiltrative astrocytomas lack the histologic features of glioblastoma (necrosis and/or microvascular proliferation) but have the molecular hallmarks of glioblastoma, including one or more of the following: EGFR amplification; gain of chromosome 7 and loss of chromosome 10; and TERT promoter mutation. In such cases, the tumor should be diagnosed as diffuse astrocytic glioma, IDH-wt, with molecular features of glioblastoma, WHO grade 4. Because these tumors have similar clinical outcomes as typical grade 4 glioblastomas, they may be treated as such with standard therapy."
- "Recommendation: 1p19q testing is an essential part of molecular diagnostics for oligodendroglioma."
- While this is most often assessed by FISH or PCR, array-based testing or NGS may also be used.

World Health Organization

The World Health Organization (WHO, 2021) classification of tumors of the central nervous system stated:[3]

- "Because of the growing importance of molecular information in CNS tumor classification, diagnoses and diagnostic reports need to combine different data types in a single "integrated" diagnosis. Such integrated diagnoses are implicit in the use of WHO CNS5…Thus, to display the full range of diagnostic information available the use of layered (or tiered) diagnostic reports is strongly encouraged…Such reports feature an integrated diagnosis at the

top, followed by layers that display histological, molecular, and other key types of information."

- "In the updated fourth edition CNS classification from 2016, the common diffuse gliomas of adults were divided into 15 entities, largely because different grades were assigned to different entities (eg, Anaplastic oligodendroglioma was considered a different type from Oligodendroglioma) and because NOS designations were assigned to distinct entities (eg, Diffuse astrocytoma, NOS). WHO CNS5, on the other hand, includes only 3 types: Astrocytoma, IDH-mutant; Oligodendroglioma, IDH-mutant and 1p/19q-codeleted; and Glioblastoma, IDH-wildtype."
- "...[A]ll IDH-mutant diffuse astrocytic tumors are considered a single type (Astrocytoma, IDH-mutant) and are then graded as CNS WHO grade 2, 3, or 4. Moreover, grading is no longer entirely histological, since the presence of CDKN2A/B homozygous deletion results in a CNS WHO grade of 4, even in the absence of microvascular proliferation or necrosis."
- "For IDH-wildtype diffuse astrocytic (NB: diffuse and astrocytic) tumors in adults, a number of papers have shown that the presence of 1 or more of 3 genetic parameters (TERT promoter mutation, EGFR gene amplification, combined gain of entire chromosome 7 and loss of entire chromosome 10 [+7/−10]) appears sufficient to assign the highest WHO grade. WHO CNS5 therefore incorporates these 3 genetic parameters as criteria for a diagnosis of Glioblastoma, IDH-wildtype. As a result, Glioblastoma, IDH-wildtype should be diagnosed in the setting of an IDH-wildtype diffuse and astrocytic glioma in adults if there is microvascular proliferation or necrosis or TERT promoter mutation or EGFR gene amplification or +7/−10 chromosome copy number changes."
- "Several molecular biomarkers are also associated with classification and grading of meningiomas, including SMARCE1 (clear cell subtype), BAP1 (rhabdoid and papillary subtypes), and KLF4/TRAF7 (secretory subtype) mutations, TERT promoter mutation and/or homozygous deletion of CDKN2A/B (CNS WHO grade 3), H3K27me3 loss of nuclear expression (potentially worse prognosis), and methylome profiling (prognostic subtyping."

Selected Relevant Publication

Ribeiro and colleagues stated in an expert-authored review (2019):[2]

- “Chromosome translocations, inversions, and insertions are frequently found in solid tumors…” however, “only few biomarkers have been approved for clinical practice that could change clinical decision making, helping in the therapeutic choices and patient management, showing the complexity of cancer and the lack of a strong bridge between the laboratory and clinicians.”

Criteria

Chromosomal microarray on solid tumor tissue may be considered in individuals who meet the following criteria:

- **Member has been diagnosed with:**
  - **Cancer of the central nervous system, or**
  - **Soft tissue sarcoma, AND**
- **Rendering laboratory is a qualified provider of service per Health Plan policy.**

References

Introduction

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