Genetics inMedicine

Section E6.5–6.8 of the ACMG technical standards and guidelines: chromosome studies of lymph node and solid tumor–acquired chromosomal abnormalities

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Cytogenetic analysis of tumor tissue is performed to detect and characterize chromosomal aberrations to aid histopathological and clinical diagnosis and patient management. At the time of diagnosis, known recurrent clonal aberrations may facilitate histopathological diagnosis and subtyping of the tumor. This information may contribute to clinical therapeutic decisions. However, even when tumors have a known recurrent clonal aberration, each tumor is genetically unique and probably heterogeneous. It is important to discover as much about the genetics of a tumor at diagnosis as is possible with the methods available for study of the tumor material. The information gathered at initial study will inform follow-up studies, whether for residual disease detection, determination of relapse and clonal evolution, or identifying a new disease clone.

This updated Section E6.5–6.8 has been incorporated into and supersedes the previous Sections E6.4 and E6.5 in Section E: Clinical Cytogenetics of the 2009 Edition (Revised 01/2010), American College of Medical Genetics and Genomics Standards and Guidelines for Clinical Genetics Laboratories. This section deals specifically with the standards and guidelines applicable to lymph node and solid tumor chromosome analysis.

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6.5 GENERAL CONSIDERATIONS

6.5.1 Genetic analysis of solid tumors and lymphomas at diagnosis provides information critical for diagnosis and patient management.[1,2] 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. Because the genetic information aids in the differential diagnosis and provides direction for the most appropriate therapeutic management, including targeted therapies, tumor 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.

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.

For disease staging, tumor samples may be accompanied or followed by other tissue samples for analysis, such as bone marrow and cerebrospinal fluid.

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6.5.2 The laboratory director and staff should be familiar with the chromosomal and molecular aberrations associated with tumor types/subtypes and their clinical significance. **Supplementary Tables S1–S5** online include common solid tumor and lymphoma chromosomal aberrations with known genes, potential FISH targets, clinical significance, and references.

6.5.3 Pediatric tumors should be cytogenetically analyzed whenever sufficient fresh tissue is available. Karyotyping, although low-resolution, provides a view of the entire genome. This genome view allows detection of cytogenetic aberrations that are commonly disease- or disease subtype–specific and have prognostic and therapeutic significance. Genetic analysis of adult tumors is indicated whenever such analysis may provide diagnostic, prognostic, or treatment-related information, especially if targeted therapies are available for the disorder undergoing study.

6.5.4 Methods for the processing of tumor material should be determined by the cytogenetic laboratory based on available clinical and pathologic findings. Laboratories should work with the oncologist and pathologist to determine the method(s) to gain the most genetic information cost-effectively. The laboratory should seek information about the suspected diagnosis and tissue type at the time of sample receipt to choose the most appropriate testing and tissue culture method(s) and to determine if DNA should be isolated from the fresh tumor. **Supplementary Table S6** online provides tumor nomenclature for tumor culture method selection.

6.5.5 Conventional cytogenetic, FISH, CMA, gene mutation panel, or sequencing analysis may be used as a primary or secondary method of evaluation of the tumor tissue. Multiple technologies may be needed for specific tumor types. The availability of fresh tissue, the differential diagnosis, a need for rapid diagnostic information, and the type of information needed should be used to prioritize testing such as conventional cytogenetic analysis, FISH, CMA, and/or mutation analysis.

6.5.6 Cytogenetic and molecular analysis results must be interpreted within the context of the pathologic and clinical findings.

6.5.7 For quality assurance, the laboratory may monitor the number and types of tumors received, the percentage of tumors with abnormal results, the cell culture success rate, and the success rate for FISH and CMA studies.

6.5.8 The presence or absence of specific aberrations should be available to the physician as soon as is feasible to contribute to the patient's plan of care.

6.6 SAMPLE COLLECTION AND PROCESSING

6.6.1 Sample collection

6.6.1.1 Tumor samples should be collected in a sterile manner. For conventional cytogenetic analysis, the tissue sample must be fresh. The sample selected for cytogenetic analysis should be "pure" tumor if possible, without necrosis. The sample must not be placed in fixative or frozen. Samples to be evaluated solely by FISH or CMA analysis may be fixed, frozen, or paraffin-embedded. If CMA analysis or sequencing is requested at the time of biopsy, DNA should be isolated from fresh tumor or formalin-fixed paraffin-embedded tumor rather than cultured tumor cells because clonal aberrations may be lost during cell culture. Cultured tumor cells may be used for isolation of DNA if the karyotype is clonally abnormal. The use of formalin-fixed paraffin-embedded samples for FISH and DNA isolation allows a pathologist to identify and mark optimal areas of tumor to examine, specify the percentage of tumor in an area, and/or identify areas of necrosis or stromal tissue to avoid.

6.6.1.2 The laboratory should request a sample size of 0.5 to 1 cm^3. If less tissue is available, the laboratory should accept as much as can be provided. If the sample size is very limited (e.g., fine needle aspirate or needle core biopsy), coverslip cultures are often successful. If the sample size precludes cell culture and conventional cytogenetic evaluation, touch preparations, cytospins, or paraffin-embedded tissue sections may be used for FISH analysis, or DNA may be isolated for CMA or sequencing analysis. See Section E6.5.2.

6.6.1.3 Fresh tumor should be transported in culture medium to the cytogenetics laboratory as soon as possible for immediate processing.

6.6.2 Sample processing

6.6.2.1 The cytogenetic laboratory should process the tumor sample as soon as possible after it is received. Prior to processing, it should be clear what methods will be used to analyze the sample (e.g., chromosome analysis, FISH, CMA, sequencing). If the sample is to be processed for CMA or sequencing, select a portion of the sample for DNA isolation. If the sample is for FISH analysis, touch preparations may be made or direct harvest performed. If the sample is for chromosome analysis, tissue culture will be required.

6.6.2.2 The fresh tumor sample should be inspected and details of the sample size, color, and attributes recorded. The time of sample collection and the time of sample receipt in the laboratory should be documented.

6.6.2.3 The cytogenetics laboratory should expect the sample submitted by a pathologist to be most representative of the tumor as determined by gross examination. However, if the fresh sample received by the laboratory is large and appears heterogeneous, portions of the sample may be cultured separately. If obvious normal, necrotic, or vascular tissues are present, the tumor should be separated from nontumor tissue for processing. Obvious necrotic tissue should be removed to reduce enzymatic damage induced by dying cells. If the tumor cannot be distinguished from normal or necrotic tissue, caution should be exercised and the entire sample processed.

6.6.2.4 For tissues from a body region with high concentrations of bacteria (e.g., tonsils, gut), treatment of the sample prior to disaggregation with antibiotic and/or antifungal solutions and addition of antibiotic and/or antifungals to the medium may be prudent.

6.6.2.5 Disaggregation methods should be optimized for different tissue types:

a. Disaggregation of solid tumor samples for tissue culture is needed. Mechanical and/or enzymatic methods may

be used. If sufficient tumor material is submitted, both methods of disaggregation are recommended. For some tumor types, different growth characteristics can be seen with exposure to collagenase versus no exposure to collagenase. If sufficient material is available, cultures should be initiated with and without enzyme exposure.

b. Disaggregation of lymphoid tissues into single cell suspension is necessary before culture initiation. The lymphoid cells in most tissues are readily disaggregated by mechanical means such as mincing with scalpels or curved scissors. The use of these methods is often advantageous if the tissue is easily dissociated because it will keep the loss of cells to a minimum and may help minimize stromal contamination because stromal cells are often locked in fibrous connective tissues. If cells are not readily liberated by mechanical means, enzymatic digestion may be necessary. When using enzymatic digestion, the tissue must first be minced and then incubated with the enzyme solution (e.g., collagenase) for 20 minutes to 16 hours depending on how quickly cell release occurs.

6.6.2.6 Culture methods, culture medium, and culture conditions should be chosen to best support the type of tumor received.

a. The diagnosis and histopathology of a tumor can be helpful in determining culture and harvest methods. Different cell types can be expected to respond differently with growth medium, harvest method, and other factors (Table 6). If the diagnosis is unknown at culture initiation, it can be helpful to know whether the pathologist would classify the tumor as a "small round cell tumor" (SRCT), which includes lymphoproliferative disorders. SRCTs can be successfully grown in suspension, whereas non-SRCTs are best grown with monolayer (flask or coverslip) culture methods. Most, but not all, SRCTs (e.g., lymphoproliferative disorders) will also grow in monolayer culture. If adequate tissue is obtained, both culture types should be initiated for SRCTs. For very small tumor samples, coverslip cultures are recommended. Duplicate cultures should be established whenever possible.

b. For lymphoid tissues, disaggregated cells are cultured in suspension using appropriate supportive growth medium. Tumor cells are spontaneously dividing; however, mitogens may be used for lymphoid disorders to encourage proliferation of the desired cell type.

6.6.2.7 Experience with solid tumor culture will provide the laboratory with information regarding optimal growth conditions and harvest methods for different tumor types.

a. It can be helpful for the laboratory to maintain a database that documents how the different tumor types have grown and which culture and harvest conditions yield abnormal clones. This database can then be searched for optimal processing and harvesting methods for any new tumor received in the laboratory.

b. Short culture durations are preferred to optimize the mitotic index of early dividing tumor cells and to avoid growth of normal tissues. Depending on the amount of available tissue, a combination of direct, 24-hour, and/or 48-hour cultures are most often utilized for lymphoid disorders. Short-term cultures (e.g., direct or overnight cultures) may also be used in conjunction with longer-term cultures to capture actively dividing cells from solid tumors.

c. Frequent (daily) observation of cells in culture is needed to determine cell growth rate and optimal time to harvest. Tumor cells should be harvested as soon as possible upon adequate growth to capture early dividing tumor cells and to prevent overgrowth by chromosomally normal cells.

d. Conditions used for cell harvest will vary among tissue types (e.g., mitotic inhibitors) used (e.g., colcemid, velban, ethidium bromide), their concentration, and exposure duration, and they should be established by each laboratory.

6.7 ANALYTICAL METHODS

6.7.1 Conventional G-banded chromosome analysis

6.7.1.1 Cell selection. Analysis of metaphase chromosomes should include cells with both good and poor chromosome morphology when attempting to identify an abnormal clone. Once identified, clonal cells with the best chromosome morphology should be analyzed, karyotyped, and imaged to provide the most accurate breakpoint assignments.

Cells that cannot be completely analyzed because of poor morphology should be scanned for obvious structurally abnormal chromosomes and abnormal chromosome counts.

Clonal abnormalities should be documented in two independent cultures, if possible, to ensure that an in vitro culture artifact is not mistakenly identified as a clinically significant abnormality.

6.7.1.2 Analytic standards

6.7.1.2.1 Initial diagnostic studies

a. Analysis
   i. Analyze 20 metaphase cells and/or a sufficient number of cells to characterize all abnormal clones and subclones.
   ii. If all cells show a complex karyotype where each cell is different, then analyze at least 10 cells with karyotyping.

b. Documentation
   i. For abnormal cells:
      1. If only one abnormal clone is present: two karyotypes.
      2. If more than one related abnormal clone is present: at least one karyotype of the stemline and at least one of each sideline.

3. If unrelated clones are present: at least one karyotype for each stemline and one for each associated pertinent sideline.

ii. For normal cells:
1. If only normal cells are present: two karyotypes.
2. If normal and abnormal cells are present: one karyotype of a normal cell plus karyotypes for abnormal clone(s) as described.

6.7.1.2.2 Follow-up studies may be performed to assess stage of disease at the time of diagnosis or at the time of tumor recurrence.

a. Analysis
   i. Analysis should include a minimum of 20 metaphase cells.
   ii. Additional cells may be scored for a specific abnormality identified in the diagnostic sample.
   iii. In addition to looking for the known clonal aberration(s) from the diagnostic study, analysis of a sample after therapy should be performed with awareness of the possibility of new aberrations signifying clonal evolution and/or a new clonal process (i.e., therapy-related malignancy).
   iv. FISH analysis may be considered in lieu of conventional chromosomal analysis for diagnoses characterized by an abnormality for which FISH testing is available.
b. Documentation
   i. If both normal and abnormal cells or if only abnormal cells are present:
      1. One or two karyotypes from each abnormal clone with a minimum of two karyotypes.
      2. One karyotype of a normal cell, if a normal karyotype was not documented in a previous study.
      3. If only normal cells are present: two karyotypes.

6.7.2 FISH analysis

6.7.2.1 FISH analysis may be used for primary, supplementary, or follow-up evaluation

a. As a primary method for tumor evaluation, FISH is useful when (i) fresh tumor tissue is not available; (ii) rapid diagnostic information is needed to narrow the differential diagnosis; (iii) gene amplification or rearrangement for diagnostic or prognostic and/or therapeutic purposes is to be determined; (iv) no metaphase cells are obtained by culture of tumor material; or (v) conventional cytogenetic analysis yields a normal result.
b. Supplemental FISH may be used as an adjunct to the initial conventional chromosomal analysis or CMA analysis to: (i) document a specific molecular event (e.g., gene rearrangement or fusion); (ii) provide a rapid result to aid in the differential diagnosis or planning of therapy; (iii) to assess gene copy number,; (iv) clarify level of clonality; or (v) confirm a microarray variant.
c. Follow-up FISH studies may be indicated to assess recurrent disease or disease progression and/or to differentiate recurrence of a tumor from a new disease process.
   i. If initial studies failed to identify the clonal process unique to the tumor, then follow-up studies may provide another opportunity.

6.7.2.2 Characterization of interphase FISH aberrations and FISH signal patterns. Characterization of interphase FISH aberrations and the FISH signal patterns in diagnostic samples is useful for future monitoring of disease. Gene fusions may confirm a specific tumor diagnosis. If a particular patient's tumor has a unique FISH signal pattern, documentation of the pattern at diagnosis can prevent misinterpretation of FISH analysis at follow-up.

6.7.2.3 Sample types. Sample types that may be used for FISH include (i) paraffin-embedded tissue sections; (ii) touch preparations (TP); (iii) cytospin preparations; (iv) cultured or direct harvest tumor cells; (v) fixed cytogenetically prepared cells; or (vi) fresh-frozen tumor tissues.

a. Paraffin-embedded tissue[3]
   i. Before scoring a paraffin-embedded FISH slide, it is crucial for a pathologist to review a hematoxylin and eosin–stained slide and delineate the region of tumor cells that should be scored because it can be difficult to differentiate normal cells from malignant cells using only DAPI counterstain. The technologist should be clear, before scoring the slide, where the malignant cells of interest are located on the slide.
   ii. Formalin-fixed, paraffin-embedded tissue is acceptable for FISH analysis. Tissues preserved in B5 fixative or decalcified are not suitable for FISH.
   iii. Tumor sections cut 3 to 4 μm thick and mounted on positively charged organosilane-coated (silanized) slides work well. The cytogenetics laboratory should request several unstained sections and one hematoxylin and eosin–stained sequentially cut section from the submitting laboratory.
b. Touch preparations
   i. A pathologist should make the TP or should be involved in selecting the tissue for TPs.
   ii. TPs are helpful when tissue architecture is not crucial.
   iii. TPs should be made by lightly touching the piece of tumor to a glass slide without smearing, followed by air drying.
c. Cytospin preparations
   i. Cytospin preparations are useful for a concentration of samples with very low cellularity (e.g., cerebrospinal fluid).
d. Fixed cytogenetically prepared cells
   i. Such preparations have multiple uses for both interphase and metaphase FISH evaluation including confirmation and clarification of suspected

chromosome aberrations or characterization of an apparently abnormal clone. Metaphase cell evaluation may help clarify specific chromosome rearrangements.

e. Fresh-frozen tumor tissues
   i. Such tissues may be useful in sequential analysis of recurring tumors or in evaluation of archived samples.

6.7.2.4 Documentation. Analysis and documentation of FISH results should be in accordance with Section E9 of these Standards and Guidelines for Clinical Genetics Laboratories.[4]

6.7.3 CMA analysis

6.7.3.1 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. Single-nucleotide polymorphism probes allow detection of large regions of loss of heterozygosity, which may harbor tumor-suppressor genes.[5]

6.7.3.2 Sample types that may be used for CMA analysis include (i) fresh tumor tissue; (ii) paraffin-embedded tumor tissue; (iii) frozen tumor; and (iv) cultured cells, chromosomally characterized when possible.

a. Fresh tumor tissue
   i. If the tumor is homogeneous, fresh tumor is the optimal sample for CMA and can be procured at the time of sample processing for chromosomal analysis. A small piece of identified tumor should be transferred to the microarray laboratory as soon as possible for DNA isolation. For heterogeneous tumors with areas of necrosis, normal tissue, or prominent stoma, DNA isolation from histologically characterized formalin-fixed paraffin-embedded material may be needed to ensure that isolated DNA is from the tumor.
b. Paraffin-embedded tumor
   i. A pathologist should review the hematoxylin and eosin-stained section of the tumor to identify an area of concentrated tumor for DNA isolation.
c. Fresh-frozen tumor
   i. Frozen stored tumor should provide high-quality DNA for CMA. A pathologist's review of the original H&E-stained slides can assure the frozen sample contains adequate tumor.
d. Cultured tumor cells
   i. Tumor cells that have been placed into culture may be used for DNA isolation and CMA as long as they remain viable. An early decision to use cells for CMA is best to minimize growth of normal tissue components.
   ii. DNA from cultured and harvested tumor cells that have been chromosomally characterized as abnormal may be used for CMA.

6.7.3.3 Documentation: analysis and documentation of CMA studies should be in accordance with Section E11 of these Standards and Guidelines for Clinical Genetics Laboratories.[5]

6.8 TURNAROUND TIME AND REPORTING

6.8.1 Turnaround time

6.8.1.1 TAT should be appropriate for clinical utility. The cytogenetics laboratory may want to have a written policy describing how tumor cases are prioritized (with respect to each other and with respect to other sample types) such that the genetic information provided can be used for patient management.

6.8.1.2 TAT guidance:

a. Because of the multiplicity of tumor types and the different tumor growth characteristics in culture, TATs will vary. However, the final report for each tumor should be available as soon as possible given such factors. Final results should be available within 28 calendar days.
b. Tumor FISH analysis results should be available within 1 to 4 days for most tumors and within 7 days for paraffin-embedded tumors.
c. Preliminary verbal reports may be appropriate for some case studies. If preliminary results are communicated, then the date of preliminary report should be documented in the final report. The content of the preliminary report should be documented if it differs significantly from that of the final report.

6.8.2 Reporting

6.8.2.1 The most recent edition of the International System for Human Cytogenetic Nomenclature should be used to report the chromosomal, FISH, CMA, and sequencing results.[6]

6.8.2.2 Cells analyzed (both normal and abnormal) should be documented in the final report.

6.8.2.3 If an aberration is suspected to be constitutional, analysis of a phytohemagglutinin (PHA)-stimulated blood sample during remission is recommended to clarify the constitutional versus clonal nature of the aberration so genetic counseling may be recommended as appropriate.

6.8.2.4 The final report(s) for tumor samples should contain the following information:

1. Patient identification using two different identifiers
2. Patient medical record number and/or laboratory identification number
3. Name of referring physician
4. Sample information (type, dates of collection and receipt, date of report)
5. Reason for referral or suspected diagnosis
6. International System for Human Cytogenetic Nomenclature of all studies performed
7. Narrative description of the aberrations observed. The report should associate results if more than one study was performed on the same tissue. The interpretation should correlate the genetic testing results with the histopathology report and patient-specific clinical information.

Discussion can include the clinical significance of the results for the diagnosis, prognosis, and/or therapeutic management of the patient with reference to current literature.

8. Literature references should be included to support the interpretation and to provide helpful information for the health-care provider.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/gim

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DISCLOSURE

All of the authors direct clinical cytogenetics laboratories that run the tests discussed in the current standards and guidelines on a fee-for-service basis.

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Supplemental Table 1. Central Nervous system tumors with diagnostic or clinically significant chromosome aberrations				
Tumor	**Chromosome Aberrations**	**Genes Involved**	**Significance**	**References (PMID)**
PEDIATRIC TUMORS				
• **GLIAL** - **Pilocytic astrocytoma grade I**	Most are normal; Loss 19p most common; Gain:5, 6, 7, 8, 9, 11,12,15, 17, 19, 20, 22; Loss: 9q, 22q	*KIAA1549/BRAF* dup *BRAF* 7q34, amp*HIPK2* 7q34	*BRAF* dup prognosis variable; More common in cerebellum than supratentorial; Often with *NF1*, benign, non-aggressive	17086101 18716556 25664944 26378811 19016743
- **Diffuse astrocytoma grade II**	Rearrangement: 2p, 7q Gain: 7q, 8q Loss: 19p	*MYBL1*	Germline mutations of *TP53*	15269292 25461780 25664944 26061751 23633565
- **Anaplastic astrocytoma grade III**	Gain: 1q, 5q, 7q; Loss: 6q, 9p, 10q, 12q, 13q, 17p, 22q; Mutation:*TP53*	*FGFR1* *CDKN2A/B* *SMARCB1*	Gain of 1q may correlate with worse prognosis	11290570 25461780 25231549 25727226
- **Glioblastoma**	Gain: 1p, 1q, 2q, 3q, 7p, 16p, 17q, 21q Loss: 6q, 8q, 10q, 11q, 13q, 16q, 17q,22q	*EGFR* *CDKN2A/B* *PTEN, IDH1, IDH2*	Amplification of genes worse outcome; *IDH1, IDH2* mutations longer survival; H3 mutations poor prognosis; Gain 3q, changes in 7, 10, 9p, 13q, 19 associated with glioblastoma progression	22064882 11290570 25461780 25727226 25752754 25231549 25754088 26328271
- **Diffuse intrinsic pontine glioma**	Gain: 1q, 7p, 7q Loss: 10q	*ampMYCN, MDM4, PDGFRA, EGFR, IRS2* *CDKN2A, PTEN*	Poor prognosis	22064882 23293772 24705252
• **MENINGIOMA**	Loss: 22q most common Loss: 1p, 14 as progresses, then loss of 4p, 6q, 7p, 10q, 11p, 18q, other whole arm loss	*NF2* mutations *Loss CDKN2A/B*	Loss 1p and other whole arm loss seen with progression / higher grade, additional losses as progresses further	20015288 23528542 21988727
• **EPENDYMOMA**	Rearrangement: 11q13.1 Gain: 1q, 7, 9	*amp ERBB2* Loss or	Gain 1q, homozygous loss	15269292 20516456

	Loss: 6q, 9p, 10, 11q, 13q, 17p, 19q	mutation*NF2, TP53, MEN1*	*CDKN2A* poor survival; Gain 9, 15q, 18, loss 6q favorable survival	24553141 24939246 20425037 21840481
- **Spinal**	Loss: 22q	homozygous loss *NF2* Loss *MEN1*	More common in adults	23528542
- **Intracranial**	Rearrangement: 2p Gain: 1q Loss: 6q23, 22q		Loss 6q have longer survival; Gain 1q poor survival, more common in pediatrics	24939246 20516456
• **MEDULLOBLASTOMA**	amp *MYCN, MYC* i(17)(q10) Loss: 10q	*ampMYCN, MYC; BRCA2, ERBB2, SUFU, ERRB4, PTCH, APC*mutations	amp *MYCN, MYC* worse outcome	15269292 20425037 22358457 24264598 20823417
- **WNT pathway**	Loss: 6, 6q	*CTNNB1, AXIN1, APC*	Very good prognosis, more common in children	22134537 19255330 24493713 22358457
- **SHH pathway**	amp *GLI2, MYCN* Gain: 3q Loss: 9q, 10q	*GLI2, MYCN PTCH1, SMO, SUFU,*	Good in infants, intermediate in children and adults	22134537 26195713 24651015 12068298 24077351
- **Group 3**	amp *MYC* Gain: 1q, 7, i(17)(q10), 18q Loss: 5q, 8, 10q, 11p, 16q	*amp MYC*	Poor prognosis, not seen in adults	22134537 19255330 22832581 25043047
- **Group 4**	amp *CDK6, MYCN* Gain: 7, 17q, i(17q), 18q, Loss: X, 8, 11p	*amp CDK4, MYCN*	Intermediate prognosis, mostly in children	22134537 19255330 22832581 25043047
• **CHOROID PLEXUS**				
- **Carcinoma (CPC)**	Gain: 1, 4, 7, 12p, 12q, 20p, 20q Loss: 3q22, 5p, 5q, 6p21, 18p, 18q, 22q	*PDGFR* *SMARCB1, TP53*	>36 mo of age more gains, <36 mo of age more losses, Loss 12q shorter survival; Mutation *TP53*more aggressive; Gain 9 and loss 10 associated with	24478045 23172371 11891207 9242217

			prolonged Survival	
- **Papilloma (CPP)**	Gain: 5p, 5q, 6q, 7p, 7q, 8q, 9p, 12, 14, 20 Loss: 10q	*PDGFR, TWIST1, TP53, NOTCH2, NOTCH3*		23172371 11891207 12237235 24478045 9242217 25575132
- **Supratentorial primitive neuroectodermal (sPNET)**	ampPDGFRA, MYB, KIT Gain: 1q, 9q, 15, 18 Loss: 9, 13q, 19q Homozygous loss: CDKN2A/B	*ampPDGFRA, KIT, MYB;* Mutation or loss *TP53, PTEN CDKN2A/B*	del 9p21.3 correlates with metastasis	20425037
- **Atypical teratoid/rhabdoid (AT/RT)**	Loss: 22q	*SMARCB1*	Distinguish from other tumors	23074045
ADULT TUMORS				
• **GLIAL**				
- **Grade I**	Gain: 7, 19, 20 Loss: 10, 22, X or Y			15269292 26061751
- **Diffuse astrocytoma, Grade II**	Loss: 17p (*TP53)*, 17q (*NF1),* 6q, 13q, 22q	*TP53, ATRX IDH1, IDH2, RB1*	Survival of ~7 years	15269292 25664944 26061751
- **Anaplastic, Grade III**	Gain: 1q, 7p, 7q, 8p Loss: 1p, 6q, 9p, 10p, 10q, 13q, 14, 17p, 19q, 22	*ampEGFR, MDM2; CDKN2A/B, PTEN, TP53, RB1, IDH1, IDH2,*	Survival of ~4 years	15269292 11290570 26061751
- **Glioblastoma, Grade IV**	amp *PIK3C2B, MDM4, EGFR*, *MET*, *MYC, CDK4, GKI1, MDM2* Rearrangement: 1, 6, 7, 9, 11, 13, 16, 19 Gain: 4q, 7p, 7q, 19, 20q Loss: 1p, 6q, 9p 10p, 10q, 13q, 17p, 22q Homozygous loss *TP73, LRRC47, DFFB*, *CDKN2A/B, CACNA1B*	amp *MDM2*,*CDK4* amp*EGFR,* *PTEN, RB1, TP53* *CDKN2A/B, TP73, LRRC47, DFFB*	Short term survival, aggressive tumor, associated with *PTEN* loss, amp *EGFR*	11290570, 19609742 25461780
• **OLIGODENDROGLIAL**	der(1;19)(q10;p10)	*FUBP1*	Favorable outcome with	15269292

	Rearrangement: 4, 6, 7, 11, 13, 15, 18, 22 Loss: 1p, 4p, 4q, 9p, 13q, 18, 19q Mutation *IDH1*	*CDKN2A/B, CIC* *IDH1, IDH2*	der(1;19); Malignant progression with amp*CDK4*, or homozygous loss of*CDKN2A/B* or *RB1*	17047046 24918277 25664944 26061751
• **OLIGOASTROCYTIC**	der(1;19)(q10;p10)	*IDH1, IDH2*	Favorable outcome with der(1;19) and/or *IDH1, IDH2*	22039037 25143301
• **MENINGIOMA**	Gain: 1q25-32 Loss: 22; Higher grade loss 1p, 6q24-qter, 9p, 10, 14q, 18q	*NF2, CDKN2A/B*	*NF2* loss or mutation homozygous loss *CDKN2A/B* with progression; Loss 6q and 14q common in recurrent tumors	20015288 23528542 25347344
• **EPENDYMONA**				
- **Spinal**	Gain 5p, 7, 12. Loss 6p, 13, 14q, 10 Mostly deletions, del22q	*NF2*	More common in adults, better survival than intracranial	24939246 23528542
- **Intracranial**	3 groups: 1) gain 9, 15q, 18 or loss 6 2) balanced or one abnormality 3) gain 1q, loss *CDKN2A/B*	*CDKN2A/B*	1) good prognosis 2) intermediate risk 3) poor prognosis	24939246 21840481 20516456
• **CHOROID PLEXUS**				
- **Papilloma (CPP)**	Gain 5q, 6q, 15q, 18q Loss 22q	*ARL4A*	Indolent	12237235 11891207 23172371 24478045 25575132
- **Atypical (aCPP - grade II)**	Gain: 7, 20, 9, 12, 8, 18, 11, 15, 19 Loss: very few	*ARL4A*	Indolent	25575132
- **Carcinoma (CPC - grade III)**	Loss**:** 3, 6, 11, 16, 17p, 22q	*TP53, GTPBP2 RSPH9, VEGFA, RBFOX1*	aggressive, poor outcome, with del/mutation *TP53* worse prognosis	25575132

Supplemental Table 2. Genitourinary tumors with diagnostic or clinically significant chromosome aberrations				
Tumor	**Chromosomal Aberrations**	**Genes Involved**	**Significance**	**References (PMID)**
RENAL				23161685
• **Renal cell carcinoma (RCC)**				
- **Clear cell RCC**	der(3)t(3;5)(p11p21;q11q35) Gain: 5q, 7, 12, 20 Loss: 3(3p12p14, 3p21 and 3p25), 4p, 5q, 8p, 9p(p13p22), 13q, 14q, Y	*VHL, PBRMI, PTH1R, IGH*	Loss 3/3p with gain 5q favorable prognosis; Loss 3/3p and loss 5q correlated with metastasis	19124809 15122209 12407697
- **Papillary RCC**	Gain: 7, 12, 16, 17, 20 Loss: 9p(p21.3), Y	*CDKN2A, MET*	Adult papillary RCC	15122209 12407697
- **t(X;V)(p11.23;V) RCC**	t(X;1)(p11.23;q23.1) t(X;1)(p11.23;p34.3) t(X;17)(p11.23;q25.3) t(X;17)(p11.23;q23.1) inv(X)(p11.23q13.1)	*PRCC/TFE3* *SFPQ/TFE3* *ASPSCR1/TFE3* *CLTC/TFE3* *NONO/TFE3*	More common in pediatric RCC; Balanced t(X;17) in RCC vs unbalanced t(X;17) in ASPS	15122209 12407697
- **t(6;11) RCC**	t(6;11)(p21.1;q13.1)	*TFEB/ALPHA*	Pediatric/young adult RCC	15644781
• **Chromophobe**	Loss: 1, 2, 6, 10, 13, 17, 21 (monosomies)		Distinguish from oncocytoma	15122209
• **Oncocytoma**	t(5;11)(q35;q13.3) t(9;11)(p23;q13.3) Gain: 7 Loss: 1(1p), 14, Y	*CCND1*	Benign; Distinguish from chromophobe; Chromosome 1 abnormality more common in bilateral tumors	15122209 12407697
• **Wilms tumor (Nephroblastoma)**	der(16)t(1;16)(q10;p10) Gain: 1q,6, 7, 8, 12, 13, 18 Loss: 1p, 7p, 11p13, 16q, 17p, 22	*TP53, WT1, WTX, CTNNB1* mutations	Unfavorable histology; Augmented chemotherapy if loss 1p, 16q	21248786 12407697 11835232 21882282
• **Clear cell sarcoma (CCSK)**	t(10;17)(q22.3;p13.3)	*YWHAE/FAM22E*	t(10;17) in 12% of CCSK; t(10;17) also in endometrial stromal cell sarcoma	22294382
• **Congenital mesoblasticnephrom**	t(12;15)(p13.2;q25.3)	*ETV6/NTRK3*	Diagnostic	12407697 11801301

a (CMN)	Gain: 11, 17, 20			
• **Rhabdoid tumor (RTK)**	Loss: 11p15.5, 22 (22q11.23)	*SMARCB1*	Diagnostic; 11p loss may be secondary to 22q loss	8824720 12407697
• **Mucinous tubular and spindle cell carcinoma (MTSCC)**	Loss: 1, 4, 6, 8(8p), 9(9p), 13, 14, 15, 22		Favorable prognosis	12429795
• **Bellini duct carcinoma (Collecting duct carcinoma)**	Gain: 3 Loss: 1 (1q32), 6 (6p), 8p, 14, 15, 21q, 22	*FH*	Aggressive	12407697 15122209
• **Papillary adenoma**	Gain: 7, 17 Loss: Y		Distinguish from papillary RCC	12407697
PROSTATE				
- **Adenocarcinoma**	del(21)(q22.2q22.3) t(7;21)(p21.2;q22.3) t(17;21)(q21.31;q22.3) t(3;21)(q27.2;q22.3) t(8;21)(q24.22;q22.2) t(7;V)(p21.2;V) t(17;V)(q21.31;V) t(3;V)(q27.2;V) t(4;6)(q22;q15) Gain: 7 (7q31), 8q24 Loss: 8p21.3, 10q23.31, 13q, 17p13.1	*TMPRSS2/ERG* *TMPRSS2/ETV1* *TMPRSS2/ETV4* *TMPRSS2/ETV5* *NDRG1/ERG* *ETV1* *ETV4* *ETV5* *MYC, PTEN, TP53,LPL*	*ERG* amp *TMPRSS2/ERG* fusion+ poor OS *PTEN*-, *TP53*-poorest OS; Hormone independence and poor prognosis with gain 8q	23161685 18563191 18563191 17437846 12837920 19402094
BLADDER				23161685
- **Urothelial cell carcinoma (Transitional cell carcinoma)**	Gain: (Pseudodiploidy/pseudotetraploidy) Loss: 8p21.3, 9 (9p21.3), 11 (11p), 13q, 14q, 15q, 17p	*LZTS1*, *CDKN2A*	Loss of 9/9p early event; Homozygous deletion *CDKN2A* higher grade & stage; recurrence, progression; Loss 8p, 11/11p, 13q, 14q, 17p and tetraploidy late stage/invasive	16110317 11888856

- **Bladder squamous cell carcinoma**	Gain: 7 Loss: 3p, 8p, 9 (9p), 17p		Loss 9/9p also early event	11888856
REPRODUCTIVE				
- **Endometrial stromal cell sarcomas**	t(7;17)(p15.2-15.1;q11.2) t(6;7)(p21.32;p15.2-15.1) t(6;10)(p21.32;p11.22) t(6;10;10)(p21.32;q22;p11.22) t(10;17)(q22.3;p13.3)	*JAZF1/SUZ12JAZF1/PHF1* *EPC1/PHF1* *YWHAE/FAM22E*	Distinguish from non-EST uterine tumors; t(10;17) also common in renal clear cell sarcoma	21420714 24342291
- **Endometrial carcinoma**	i(1q) Gain: 1q, 2, 7, 10		More complex abnormalities seen in serous versus endometrioid carcinomas	7736425 9115961 8174089
- **Uterine leiomyomata**	t(6;V)(p21.31;V) or other rea(6p21.31) t(12;14)(q14.3;q23-24) del(7)(q22q23)	*HMGA1* *HMGA2*	Only 40% of uterine leiomyomata exhibit abnormal karyotypes; *MED12* mutations in ~80% of 46,XX myomas	16504804
GERM CELL (GCT)				
- **Postpubertal GCTs**	i(12p) Gain: 1q, 7, 8, 12p, 21, 22, X Loss: 1p, 4, 5, 11q, 13q, 18	*RET/NCOA4*	i(12p), amp(12p) distinguishes GCTs; Mediastinal GCT associated with Klinefelter syndrome	9461002 15738984
- **Prepubertal GCTs**	Gain: 1q, 2p, 3p, 13, 16p, 20q Loss: 1p, 4q, 6q		12p gain rare in prepubertal GCT distinguishes from adult GCT; Prepubertal GCT karyotypes generally less complex compared to adult GCTs	24577549

Supplemental Table 3. Gastrointestinal, dermal and neural crest tumors with diagnostic or clinically significant chromosome aberrations				
Tumor	**Chromosomal Aberrations**	**Genes Involved**	**Significance**	**References (PMID)**
GASTROINTESTINAL				
• **GIST**	Loss: 1p, 14q, 15q, 13q, 22q Gain: 1q, 12q	*KIT, PDGFRA*	*KIT, PDGFRA* mutation diagnostic, response to TKIs	18623623, 18671247 16452129, 15095270 12072198, 20470368 15580284, 23942094
• **LIVER**				
- **Hepatoblastoma**	Gain: 1q, 2, 2q, 8, 20, der(4)t(1;4) Loss: 4q	Unknown genes	Distinguish from HCC, HMH	15981236, 20461752 25525853
- **Hepatic mesenchymal hamartoma (HMH)**	t(11;19)(q13;q13.4) t(19;V)(q13.4;V)	Unknown genes	Distinguish from hemangioma or malignant tumor	15325096
• **SALIVARY GLAND**				
- **Pleomorphic adenoma**	t(3;8)(p22.1;q12.1), t(12;V)(q14.3;V) Gain: 8	*CTNNB1/PLAG1, HMGA2*	Diagnostic; benign tumor	17693184, 15920557 18828159, 20055685 22987447
- **Ca-ex-PA**	*HMGA2, MDM2* amplification	*HMGA2, MDM2*	Amplification contributes to malignant transformation of PA	15920557, 22287457 22297681
- **Mucoepidermoid cancer**	t(11;19)(q21;p13.11) in 40-80%; Gain: 7, 8, X Loss: 6q	*CRTC1/MAML2*	Malignant; t(11;19) assoc with low / intermediate grade tumors	18486532, 16444749 23583282, 22847156
- **Warthin's tumor**	t(11;19)(q21;p13.11) in low percentage	*CRTC1/MAML2*	Benign; t(11;19) w/ metaplasia	18647217
DERMAL				
- **DFSP and variants (GCF, Bednar, other)**	t(17;22)(q22;q13.1), der(22)t(17;22) or r(22)t(17;22)	*COL1A1/PDGFB*	Diagnostic for DFSP; response to TKIs	20637435, 17124411 19890351, 12550751 21111450, 12661001 23327733
- **Hidradenoma**	t(11;19)(q21;p13.11), Gain: 7, 8, X Loss: 6q	*MAML2/CRTC1*	Clear cell variant	17334997, 15729701

- **Cutaneous melanoma**	Gain: 1q, 6p, 7, 8q, 11q, 17q, 20q Loss: 6q, 9, 9p, 10q	*CDKN2A, BRAF, PTEN*	*CDKN2A*	21732770, 21876842 25207365
- **Uveal melanoma**	Loss: 3 Gain: 8q	*GNA11, GNAQ*	Monosomy 3 correlates with metastatic disease	21083380, 1309305 22415057
BREAST				
- **Invasive intraductal**	dmin, hsr	*ERBB2* amp	Improved outcome with targeted therapy	19548375, 22417857 23539740
- **Secretory Breast**	t(12;15)(p13.2;q25.3)	*ETV6/NTRK3*	Favorable; distinguish from other breast lesions	22129193, 23944930
LUNG				
- **NSCLC**	*EGFR* high copy number or amplification, Loss: 3p	*EGFR*	Response to TKIs	21670455, 21400669 20472851
	Gain: 7			25492085, 25055117
	MET amplification	*MET*		25806222
	inv(2)(p21p23.2)	*EML4/ALK*	Response to TKIs	
	ALK, ROS1, RET rearrangements			22311682, 22282074 25288236, 25077070 25806222
NEURAL CREST				
- **Neuroblastoma**	del(1p) with or without *MYCN* amplification	1p	Unfavorable	22146831, 16306521, 19401703
	2p24.3	*MYCN* amp	Unfavorable	15571958, 19401703
	11q deletion	11q23 band region	Unfavorable, inversely associated with *MYCN*	16306521, 19401703
	Low *ALK* expression	*ALK*	Unfavorable	21492432
	Gain 17q with or without *MYCN* amp	17q	Unfavorable	22146831, 19171713
	del(3p)	In assoc with del(11q), lack *MYCN* amp	Older age at diagnosis, unfavorable	12538451, 15800319
	Triploidy without above aberrations		Favorable	19401703

amp-amplification; Ca-ex-PA-Carcinoma ex Pleomorphic Adenoma; DFSP-dermatofibrosarcoma protuberans; dmin-double minutes; GCF-giant cell fibroblastoma; GIST-gastrointestinal tumor; HCC-hepatocellular carcinoma; hsr-homogeneously stained regions; NSCLC-non-small cell lung carcinoma; TKI-tyrosine kinase inhibitor

Supplemental Table 4. Bone and soft tissue tumors with diagnostic or clinically significant chromosome aberrations				
Tumor	**Chromosome Aberrations**	**Genes Involved**	**Significance**	**References (PMID)**
BONE TUMORS				
- **Aneurysmal bone cysts**	t(1;17)(p34.3;p13.2) t(3;17)(q21.3;p13.2) t(9;17)(q22.31;p13.2) t(16;17)(q21;p13.2) t(17;17)(p13.2;q21.33)	*THRAP3/USP6* *CNBP/USP6* *OMD/USP6* *CDH11/USP6* *COL1A1/USP6*	Benign lesions but locally aggressive. Recurrences are common	11408073 11441369 15044915 15735689
- **Chondrosarcoma**	Structural abnormalities: 1, 6 , 9, 12, 13, and 15 Gains and losses: 5, 7, 8, and 19		Presence of chromosome abnormalities correlates with increasing histological grade with complex aberrations mainly seen in high-grade disease 13q loss is an independent factor for metastasis, regardless of the tumor grade and size	8402563 10629543 11793445 11793371
- **Enchondroma**	Broad range of chromosomal abnormalities but chromosome 6 and 12 are more frequently affected		A common benign hyaline cartilaginous lesion	1458512 8402563 9452264 12606137 12742153
- **Osteochondroma**	Germ line losses; 8q24.11or 11p11.2	*EXT1*or *EXT2*	Most common benign bone tumor	7507706 9576285
- **Osteosarcoma**	Gains: 1q21, 3p26, 6p, 8q, 12p12p13, 14q24qter, 17p11p12, Xp12, and Xp11.2p21 Losses: 6q, 13q, and 17p	 *RB1* and *TP53*	1q21 and 8q gains are associated with shorter survival 13q and 17p losses are poor prognostic signs	8344751 8636759 9140456 9685858 11950895
- **Parosteal Osteosarcoma**	12q13q15 amplification, ring chromosomes	*CDK4, MDM2*	Low grade malignant potential	22749040 20196171
SOFT TISSUE TUMORS				
• **Adipocytic tumors**				
- **Lipoma**	Translocations involving 12q14.3 t(3;12)(q28;q14.3) most common	*HMGA2* rearrangements *HMGA2/LPP* most common	65% of cases. Distinguish from liposarcoma	1988102 8453640 8812423 9403060

				9530339
	Losses: 13q11q22, and 6p21p23 rearrangements		15-20% of lipomas without 12q14.3 rearrangements	
- **Chondroid lipoma**	t(11;16)(q13.1;p13.12)	*C11orf95/MKL2*	Diagnostic	20607705
- **Lipoblastoma**	Rearrangements involving 8q12.1 Gains: 8 with or without 8q12.1 rearrangements	*PLAG1* rearrangements	Rare benign soft tissue tumor of embryonal fat	10987300 11549588
- **Liposarcoma**				
a) Well-differentiated liposarcoma	Ring and giant marker chromosomes usually involving 12q14q15	*MDM2, CDK4,* and *HMGA2* amplification	Low-grade malignancy that may recur locally but doesn't metastasize	1568170 8353809 8387391
b) Myxoidliposarcoma	t(12;16)(q13.3;p11.2)	*FUS/DDIT3*	Diagnostic	7503811 7805034 8510758
c) Pleomorphic liposarcoma	Complex karyotypic changes with no characteristic abnormalities		Highly malignant tumor	9591630
- **Spindle cell lipoma/Pleomorphic lipoma**	Losses: 2q21, 6q14q21, 10p, 13q, 16q22qter, and 17p		Distinguish from liposarcoma	7798294
• **Fibroblastic/Myofibroblastic tumors**				
- **Angiofibroma**	t(5;8)(p15.33;q13.3)	*AHRR/NCOA2*	Diagnostic. Benign tumor with local recurrence	22337624
- **Adult fibrosarcoma**	Complex karyotypes with no consistent abnormality detected			
- **Infantile fibrosarcoma**	t(12;15)(p13.2;q25.3) Gains: 8, 11, 17, and 20	*ETV6/NTRK3*	Diagnostic	1582636
- **Inflammatory myofibroblastic tumor**	t(1;2)(q21.3;p23.2) t(2;2)(p23.2;q12.3) t(2;17)(p23.2;q23.1) t(2;19)(p23.2;p13.12)	*TPM3/ALK* *RANBP2/ALK* *CLTC/ALK* *TPM4/ALK*	Rare soft tissue tumor at the edge between benign and malignant	10383129 10934142 12112524 12661011
- **Low-grade fibromyxoid sarcoma**	t(7;16)(q33;p11.2) in 70% of cases	*FUS/CREB3L2* associated with	Diagnostic	11106828 12960807

	Supernumerary ring chromosome in 25% of cases	both abnormalities		
- **Solitary fibrous tumor**	12q13 rearrangements	*NAB2/STAT6*	Diagnostic	23761323
• **Smooth muscle tumor**				
- **Leiomyosarcoma**	Complex karyotypes with no consistent abnormality detected	Involvement of *TP53, FANCA, RB1, PTEN,* and *ROR2*		8622088 12827608
• **Skeletal muscle tumors**				
- **Alveolar rhabdomyosarcoma**	t(2;13)(q36.1;q14.11) t(1;13)(p36.13;q14.11) Amplifications: 1p36, 2p24, 2q34qter, 12q13q15, 13q14, and 13q31	*PAX3/FOXO1* *PAX7/FOXO1*	Diagnostic translocations	8098985 8275086 11607823 12039929
- **Embryonal rhabdomyosarcoma**	Complex karyotypes with gains: 2, 8, and 13 Loss of heterozygosity at 11p15.5			8764111 12506174 18985676
- **Spindle cell or sclerosing rhabdomyosarcoma**	t(6;8)(q22.1;q13.3) t(8;11)(q13.3;p15.3)	*VGLL2/NCOA2* *TEAD1/NCOA2*	Congenital/infantile rhabdomyosarcoma	26501226 23463663
• **Tumors of uncertain differentiation**				
- **Angiomatoid fibrous histiocytoma**	t(12;16)(q13.12;p11.2) t(12;22)(q13.12;q12.2) t(2;22)(q33.3;q12.2)	*FUS/ATF1* *EWSR1/ATF1* *EWSR1/CREB1*	Diagnostic translocations	15884099 17188428 17724745 18094413
- **Alveolar soft part sarcoma**	der(17)t(X;17)(p11.23;q25.3)	*ASPSCR1/TFE3*	Diagnostic	1423174 11169942 11244503
- **Clear cell sarcoma of the soft tissue**	t(12;22)(q13.12;q12.2)	*EWSR1/ATF1*	Diagnostic	8401579 8552387
- **Desmoplastic small round cell tumor**	t(11;22)(p13;q12.2)	*EWSR1/WT1*	Diagnostic	1314522 8374894 8187063
- **Ewing sarcoma**	t(11;22)(q24.3;q12.2)	*EWSR1/FLI1*	90% of cases	3163261

	t(21;22)(q22.2;q12.2) t(7;22)(p21.2;q12.2)	*EWSR1/ERG* *EWSR1/ETV1*	Variant translocations in 5% of cases	1522903 8022439 7700648
- **Undifferentiated small round cell sarcoma**	t(4;19)(q35.2;q13.2) t(10;19)(q26.3;q13.2) t(X;19)(q13.1;q13.2) inv(X)(p11.4p11.22)	*CIC/DUX4* *CIC/DUX4L3* *CIC/FOXO4* *BCOR/CCNB3*	*EWSR1* negative, aggressive	25683183 25007147 24215322
- **Extraskeletal myxoid chondrosarcoma**	t(9;22)(q22.33;q12.2) t(9;17)(q22.33;q12) t(9;15)(q22.33;q21.3)	*EWSR1/NR4A3* *TAF15/NR4A3* *TCF12/NR4A3*	Diagnostic translocations	3967207 10602520
- **Extrarenal rhabdoid tumor**	Germ line deletions or translocations involving 22q11.23	*SMARCB1*	Poor prognosis	8092393 8545590 9892189 26216536
- **Synovial sarcoma**	t(X;18)(p11.23;q11.2) t(X;18)(p11.22;q11.2)	*SS18/SSX1* *SS18/SSX2*	Diagnostic translocations	3461881 3030536 3030537 7951320 9428816

Supplemental Table 5. Lymphomas with diagnostic or clinically significant chromosome aberrations				
Tumor	**Chromosomal Aberrations**	**Genes Involved**	**Significance**	**References (PMID)**
• **B-CELL**				
- **Burkitt lymphoma**	t(8;14)(q24;q32) t(2;8)(p12;q24) t(8;22)(q24;q11.2)	*IGH/MYC* *IGK/MYC* *IGL/MYC*	Characteristic *MYC* disruption Variant translocations	4113130 946170
	Gain: 1q21-q25, 7, 8, 12, 13q, 18 Loss: 6q, 13q, 17p		Secondary changes /Unfavorable: 13q	18923440 1869243 21207210 19895612
- **Diffuse large B-cell lymphoma (DLBCL)**	t(3;14)(q27;q32) t(2;3)(p12;q27) t(3;22)(q27;q11.2)	*IGH/BCL6* *IGK/BCL6* *IGL/BCL6*	Characteristic*BCL6* disruption, variant translocations	8235596 8506375
	Gain:X, 3, 5, 7, 9, 12, 18, 1q23-q31, 1q31-q44, 3q, 6p, 7p, 7q31-q32, 8q2-2q24, 11q12-q13, 12q14-q24, 18q11q21, 22q12-qter		Unfavorable: 3, 1q Favorable: 5, 7q	11850073 15350300 10337996 12181265 21418177
	Loss: Y, 4, 6, 13, 15, 17, 1p36pter, 2p23pter, 4q32qter, 6q21q25, 8p12pter, 9p21pter, 11q23qter, 12p12p13, 14q23qter, 17p12p13, 18q21qter	*CDKN2A,TP53*	Unfavorable: 9p, 17p	18765795 20813005 17881637
	Rearrangement: 4p13, 6p22, 7p13, 8q24, 11q23, 13q14, 15q22, 17q11, 18q21	*MYC* *BCL2*	Unfavorable: *MYC* disruption *BCL2* disruption	21490439 24740248 22189900 15215171
- **Follicular lymphoma**	t(14;18)(q32;q21) t(2;18)(p12;q21) t(18;22)(q21;q11.2)	*IGH/BCL2* *IGK/BCL2* *IGL/BCL2*	Characteristic *BCL2* disruption, Variant translocations	7579360 2129304
	Gain: X, 3, 5, 7, 8, 12, 18 (18q)		Unfavorable: X, 7, 12, 18, der(18)t(14;18)	10389925 8049424
	Loss: 1p36, 6q21, 6q23q26, 9p21, 10q22q24, 17p13	*CDKN2A, PTEN,TP53*	Unfavorable: 6q, 9p21, 10q22-q24, 17p13	9087572 9616165 17699855
	Rearrangement: 1p, 3q27, 6q23q26, 8q24, 11q, 12q13q15	*BCL6* *MYC*	*BCL6* disruption Unfavorable: *MYC* disruption	8167331 16075463 14736281
- **Mantle cell lymphoma**	t(11;14)(q13;q32)	*IGH/CCND1*	Characteristic *CCND1*	8499640

			disruption	
	Gain:3(3q), 12(12q)		Unfavorable: 3q, 12	
	Loss: Y, 1p, 6q, 9(9p), 10q, 11q, 13q, 17p, 18	*CDKN2, TP53*	Unfavorable: 9p, 13q14, 17p	9559341 21945515
	Rearrangement:			
	t(2;12)(p12;p13)	*IGK/CCND2*		
	t(12;14)(p13;q32)	*IGH/CCND2*		16861358
	t(6;14)(p21;q32)	*IGH/CCND3*		18391076
	8q24, 3q27	*MYC, BCL6*	Unfavorable: *MYC* disruption, complex karyotype	15138714
- **B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)**	Gain: 3, 12, 18, 2p24p25, 3q26q27, 8q24	*MYC*	Characteristic 12 gain Unfavorable: *MYC*	11486330
	Loss: 6q, 9p, 11q22, 13q, 14q24q32, 17p	*CDKN2A, ATM IGH, TP53*	Favorable: isolated 13q14.3 deletion Unfavorable: 6q, 17p, 9p	18477041 21749360 23001040
	Rearrangement:			
	t(9;14)(p13;q32)	*IGH*		10784387
	t(11;14)(q13;q32)			23581835
	t(14;19)(q32;q13.3)			21502423
	8q24, 18q21	*MYC, BCL2*	Unfavorable: *MYC* disruption	19246886
- **Splenic marginal zone lymphoma**	Gain: 3q			11146574
	Loss: 6q, 7q31q32, 8p, 17p	*TP53*	Unfavorable: 7q, 8p/17p together	10329610 21115979 20479288 22816737
- **Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)**	t(11;18)(q21;q21)	*BIRC3/MALT1*		10979968 10907943
	t(14;18)(q32;q21)	*IGH/MALT1*		12406890
	Gain:3 (3q), 9q, 18 (18q)		Unfavorable: partial or complete trisomy 18	17606442 16512826
	Loss: 6q, 9p, 17p	*CDKN2A,TP53*	Unfavorable: 9p, 17p	17525089
	Rearrangement: 1p22, 2q, 3p14.1	*BCL10, FOXP1*		20352431 9178679 10845924 15703784
- **Nodal marginal zone lymphoma**	Gain: 3, 7, 12, 18			16405665
	Loss: 6q, 11q	*ATM*		8547655 16156859
	Rearrangement:			
	t(11;14)(q23;q32)	*IGH/DDX6*		22965301
	1q, 1p, complex karyotype			

- **Lymphoplasmacytic lymphoma**	Gain: 3, 12, 18 Loss: 6q, 7q, 13q, 17p		Unfavorable: 6q	23477936 12351413
- **Primary mediastinal (thymic) large B-cell lymphoma**	Gain: 2p15, 9p24, Xp11.4p21, Xq24q26	*REL, JAK2*		11241792 8608249 15572583 17728785
- **ALK-positive DLBCL**	Translocation: t(2;17)(p23;q23), variants	*ALK*		19521280 17509395
- **B-cell, unclassifiable** - **with features intermediate between DLBCL and Burkitt lymphoma**	Rearrangement:3q27, 8q24, 14q32, 18q21 Complex karyotypes	*BCL6, MYC, IGH,BCL2*	Unfavorable: *MYC* disruption combined with *BCL2* or *BCL6* (double hit)	23600716 25696840
- **B lymphoblastic lymphoma**	t(9;22)(q34;q11.2) t(4;11)(q21;q23), *KMT2A* variants t(12;21)(p13;q22) Gain:X, 4, 10, 14, 17, 21	*BCR/ABL1* *KMT2A/AFF1* *ETV6/RUNX1*	Unfavorable Unfavorable Favorable Favorable: 4, 10, 17	16304368 11071360 22580999 11392884
- **B or T lineage lymphoblastic lymphoma**	Rearrangement:8p11	*FGFR1*	Unfavorable	23594707
• **T-CELL**				
- **Anaplastic large cell, *ALK*–positive (ALCL) lymphoma**	t(2;5)(p23;q35), variants Gain: X, 7, 9, 17p, 17q24-qter Loss: Y, 4q13-q21, 6q, 17, 11q14, 13q	*ALK*	Favorable	25533804 18385450 20660290 18275429
- **Anaplastic large cell, *ALK*–negative (ALCL)** - **lymphoma**	Gain: 1q, 3p, 6p21, 7 Loss: 6q13p21, 13q, 15, 16pter, 16qter, 17p13			18275429 15111330
- **Angioimmunoblastic** - **T-cell lymphoma**	Gain: X, 3 (3q), 5 (5q), 11q14, 19, 21, 22q Loss: 6q, 13q Rearrangement: 1p		Unfavorable: X Unfavorable: 1p31p32, Complex karyotypes	22586046 17044049 18341637 7919378 12780782 8636776
- **Peripheral T-cell lymphoma, NOS**	Gain: 1q, 3p, 5p, 7q22q31, 8q24qter,			18341637 7987800

	11q13, 17q, 12p13, 22q Loss: 4q, 5q, 6q, 9p, 10q,11p11, 12q, 13q, t(14;19)(q11;q13), TCRA/D variants t(5;9)(q33;q22)	 *TCRA/TCRD*	 Favorable: 5q, 10q, 12q Follicular variant	8286748 10700871 15111330 17696193 17582237 16341044
- **T lymphoblastic lymphoma**	t(10;11)(p13;q14) t(7;14)(p14;q32) Loss: 9p Rearrangement: 7p14, 7q35, 14q11.2, 14q32, 11q23	*PICALM/MLLT10* *TRG,TCL1A* *CDKN2A* *TCRG, TCRB, TCRA/D, IGH, KMT2A*		16826225 24966976 17369128
- **Hepatosplenic T-cell lymphoma**	Gain: 7, i(7q), 8 Loss: X, Y			9264394 11807981 16941150
• **HODGKIN**				
- **Classical Hodgkin lymphoma**	Gain: 2p, 4p16, 4q23q24, 9p23-p24, 12q Polyploid Loss: 1p, 3p, 6q, 7q Rearrangement: 1p36, 6q15, 6q21, 7q22, 7q32, 8q24, 11q23, 12q24, 13p11, 14p11, 14q32, 15p11, 19p13 complex karyotypes	 *IGH*	 Arising from follicular lymphoma	10676635 10190942 21325169 17510532
- **Nodular lymphocyte, predominant**	Rearrangement: 3q27 Similar rearrangements as in DLBCL- Complex karyotype Gain: Polyploid	*BCL6*		15339680, 16049307 16353293

Supplemental Table 6. Tumor nomenclature for solid tumor culture method selection

Tumors types may histologically be divided into small round cell tumors (SRCTs) and non-small round cell tumors (NSRCTs) based on cellular features. SRCTs may grow in suspension or attach to the culture dish and grow as a monolayer. NSRCTs will not grow in suspension. When the sample is received in the lab, if the histopathologic diagnosis is not yet known, it can be helpful if the pathologist can tell you if the tumor is a 'SRCT' for the purposes of initiating cultures. Some tumors may grow with either method. If sufficient sample is provided for a SRCT, initiate cultures using both methods. If a very small amount of tumor is received, a coverslip culture is best. Observation of growth will allow one to determine if cells attach or float. If cells float and form balls, a suspension microharvest can be done. Suspension direct or overnight harvest may provide material for FISH if culture growth fails.

Suspension only tumors

- Lymphoma or other lymphoproliferative disorders
- Histiocytosis
- Plasmacytoma

Suspension and monolayer - Small round cell tumors

- Ewing sarcoma or peripheral primitive neuroectodermal (pPNET)
- Medulloblastoma or central primitive neuroectodermal tumor (PNET)
- Neuroblastoma
- Osteosarcoma
- Retinoblastoma
- Rhabdomyosarcoma

Monolayer Culture - Non-small round cell tumors

Brain tumors

- Astrocytoma
- Choroid plexus tumors
- Ependymoma
- Glial tumors, glioblastoma, ganglioglioma
- Meningioma
- Oligodendroglioma

Mesenchymal tumors or sarcomas or "spindle cell" tumors

- Clear cell sarcoma
- Desmoplastic small round cell tumor
- Fibrosarcoma
- Hemangiosarcoma
- Hepatoblastoma, hepatocellular carcinoma
- Leiomyosarcoma, leiomyoma
- Liposarcoma, lipoma
- Malignant fibrous histiocytoma (MFH)
- Mesothelioma
- Synovial sarcoma
- Wilms tumor

Germ cell tumors

- Embryonal carcinoma, yolk sac tumors
- Seminoma
- Teratoma

Epithelial tumors (carcinomas)

- Breast
- Gastrointestinal
- Lung
- Prostate
- Renal cell