Detecting Subtelomeric Chromosome Rearrangements by Fluorescence in Situ Hybridization (FISH).

Who should be tested?

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Most human chromosomes begin and end with a light staining band using conventional cytogenetic methods. As a result, exchanges or translocations between chromosomal ends are not detectable with such methods and molecular cytogenetic techniques such as fluorescence in situ hybridization (FISH) are used for detecting such rearrangements. FISH involves hybridizing a fluorescently tagged DNA probe that is complementary to a specific gene or chromosome region of interest. For subtelomeric FISH, the DNA probe is selected from subtelomeric regions which are located in terminal chromosomal bands adjacent to telomeres. The subtelomeric regions, unlike telomeres, are unique to a specific chromosome. Subtelomeric chromosomal rearrangements can include translocation to another chromosome, loss of a copy of the region or gain of a copy of the subtelomeric region. Studies have demonstrated that subtelomeric regions are gene-rich and imbalances in these regions either through deletion or gain can have adverse clinical effects, in particular, developmental delay, craniofacial dysmorphology and other nonspecific findings; and that carriers of balanced translocations are at risk of having children with unbalanced chromosomal complements.

What is the test and who should get it?

This FISH test involves numerous hybridizations at the subtelomeric region of each chromosome with a specific DNA probe to determine if the region is present, absent or has moved to another chromosome. Commercial probe sets exist for examining most human subtelomeric regions. Most of these probe sets are within 300,000 - 500,000 nucleotides from the ends of the chromosomes. Several, however, are a considerably greater distance from the chromosomal end and therefore are not able to detect more terminal rearrangements. A commonly used commercial FISH platform requires 15 separate hybridizations to test for all human subtelomeric regions. The testing is time consuming and costly. As a result, it is important to ensure that only the appropriate patient population is being tested.

Since many different chromosomal regions are involved in subtelomeric rearrangements, there is no defined constellation of clinical features as observed in syndromes caused by a single chromosomal region (ie. chromosome 22q11.2 and DiGeorge syndrome ). We have surveyed the medical literature for subtelomeric FISH studies in patients with abnormal clinical findings and have developed a generic but useful clinical checklist for determining the patients who are most likely to have an abnormal result on subtelomeric FISH. With this checklist, up to 10% of children with idiopathic mental retardation have been shown to possess a subtelomeric chromosomal abnormality.

In brief, for subtelomeric FISH testing - the patient should have developmental delay/mental retardation and normal chromosomes at ≥ 550 band level, as well as, features from at least two of three categories. The three categories are i) growth defect (prenatal or postnatal) in the patient; ii) dysmorphology (facial or nonfacial) in the patient; and iii) positive family history (such as mental retardation, congenital malformation, ≥ miscarriages) in family members of the patient. Once a chromosome abnormality is identified in the patient, then parental chromosome studies are usually requested to determine if the abnormality is inherited or de novo and whether there are risks of having other children with the same abnormality.

Subtelomeric FISH testing is available at CMH. Submission of the completed clinical checklist with the specimen is requested. The checklist is available from the Cytogenetics Laboratory. Please contact the Cytogenetics Laboratory at (816) 802-1220 for more information about this testing.
**The Surgical Pathology Report:**  
1) **Varifying Levels of Diagnostic Certainty** & 2) **Turn-Around-Times**  
By David Zwick

1. “What difference does it make when I see a diagnosis preceded by the words ‘consistent with….’ in pathology reports?”

Most morphologic changes lack diagnostic or etiologic specificity and hence there are few pathologic diagnoses that are rendered in an unqualified and non descriptive manner. Tissue and organs can only respond morphologically in a limited number of ways and yet there are an almost limitless number of diseases. Cancer of various types is a major category of disease in which an unqualified diagnosis is commonly rendered because the morphologic changes are sufficiently specific (i.e. “pathognomonic”). However, most biopsies are not done to verify cancer, but to confirm or enhance the certainty of clinical diagnosis, provide staging or prognostic information, or to detect and identify a pathogenic agent. The written report often reflects this uncertainty in the wording of the pathologic diagnosis.

There is a very important and implicit difference in meaning when a diagnosis is preceded by the words “consistent with” as opposed to being stated in an otherwise unqualified manner. The words “consistent with” indicate the diagnosis is qualified and predicated on some information other than the findings of the biopsy alone. Such use is most commonly based on the clinical information proved on the tissue requisition (e.g. “rule out Celiac Disease,” “Pityriasis Rosea”) or information conveyed verbally by the caregiver or extracted from the patient’s medical record.

When confronted with a situation in which the histopathologic findings are not specific, the pathologist undertakes to determine if the findings are typical or atypical of the condition suggested and, if atypical, determine if the morphologic findings are characteristic of an alternative diagnosis. Therefore, it is very helpful to provide reasonable alternative clinical diagnostic considerations. In these circumstances, there is often a descriptive diagnosis that may or may not be followed by a specific diagnosis (e.g. “Intestinal villous atrophy consistent with Celiac Disease”). Such wording as “consistent with” or even “characteristic of” should alert the clinician that there may be an alternative diagnoses that shares the same morphologic features as the condition suspected on clinical grounds.

If the information that the diagnosis was predicted on is in error, or if the patient does not respond to treatment in a manner appropriate for the stated diagnosis, the clinician should consider alternative diagnosis. Under the latter circumstances, a discussion with the pathologist who signed the case out might prove useful for redirecting the diagnostic investigation and correcting any potential misunderstandings.

2) **TURNAROUND TIME:** If I submit my biopsy today, when will I see a copy of the final report?

Unsigned reports are not electronically available for viewing. Most signed reports (>80%) are available in MEDICTECH PCI as follows:

1.) Routine cases that do not requiring special stains are completed in 2 working days from the time the biopsy is accessioned in the histology laboratory. Routine cases requiring special stains require another 1-3 working days to complete. Biopsies arriving after 4pm or on weekends or holidays are accessioned the next working day.

2.) Complex cases requiring special stains or special studies (e.g. immunofluorescent or electron microscopy, flow cytometry, etc) may take up to 7-14 days or longer. If the delay is expected, a signed report of the microscopic findings may be issued sooner with a notation that an addendum report will follow at the completion of special studies.

* If patient’s condition warrants, the pathologists may be called and provide provisional diagnostic information when appropriate.