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INVITED EDITORIAL
Multilocus FISH Analysis

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In this issue of the *Journal,* Ligon et al. (1997) have demonstrated the technical feasibility of a multilocus FISH (MultiFISH) analysis, in which simultaneous use of different probes permits detection of several different microdeletion syndromes. They propose that this methodology could be used as a screening tool for patients who present with unexplained developmental delay and/or mental retardation. They base their recommendation on cost-effective use of laboratory resources. The authors point out that such a screening tool would be useful when a clinical diagnosis is difficult to establish either because of an atypical phenotype or lack of clinician skill. The multiFISH panel that was chosen by these authors represents those disorders for which they have determined that good-quality FISH probes are available: Prader-Willi, Angelman, Williams, DiGeorge/velocardiofacial and Smith-Magenis syndromes.

There can be no doubt that FISH has greatly facilitated the diagnosis of these microdeletion syndromes—especially in young patients, in whom all necessary diagnostic findings may not yet have emerged, and in atypical patients. For example, DiGeorge/velocardiofacial syndrome has a notoriously broad phenotype, which has become even broader since the advent of molecular testing, and correct diagnosis of it on clinical grounds alone can elude even the most experienced clinical geneticist/dysmorphologist. Ligon et al. have essentially asked us to revisit the role of the clinician versus molecular testing in another instance—that is, when clinicians lack the skill to make or suspect diagnoses on clinical grounds alone. Ligon et al. have suggested that lack of clinician skill is a reason to create a panel of tests for disparate disorders. In contrast, it is the opinion of many—as it has been, even from the earliest days of molecular-genetic testing—that the clinician plays a central role in the appropriate use of highly focused molecular-diagnostic laboratory testing. Through the clinician's use of the medical history, family history, and physical examination, the patient effectively undergoes a "genomewide scan" for a possible heritable disorder, following which the clinician uses laboratory testing to support or refute his or her diagnostic impressions. When disorders have overlapping phenotypes that may not be readily distinguishable clinically, simultaneous use of diagnostic tests is appropriate. For example, cytogenetic fragile X testing was offered along with routine cytogenetic testing for years prior to discovery of the FMR1 gene. More recently, fragile X DNA testing has been combined with routine cytogenetics for screening younger boys and females of all ages who have developmental delay and/or mental retardation. Currently, some laboratories are offering panels of molecular genetic tests for neurological disorders, such as spinocerebellar ataxia type I, spinocerebellar ataxia type III, Huntington disease, and DRPLA, in which the phenotypes are similar.

In contrast to these situations, it is more difficult to argue for the use of a panel of tests for disorders that do not have significantly overlapping features and that would not be considered in the differential diagnosis of the same patient by a skilled clinician. In my experience, it would be a most unusual patient in whom a medical geneticist would sequentially order testing on the five disorders proposed in the panel presented by Ligon et al. Thus, simultaneous use of these five FISH tests does not appear to address a recognized clinical need.

A significant concern about genetic testing of any sort derives from the common misperception that a normal result is an indication that "there is no genetic problem." For example, clinical geneticists hear this refrain repeatedly from patients, families, and physicians who believe that a normal cytogenetic study has ruled out a genetic basis for their concerns. Recent studies have shown that clinicians who have a poor understanding of the nature and limitations of a genetic test that they have ordered may also have difficulty conveying the results accurately (Giardiello et al. 1997). It is easy for medical geneticists to see how the normal results of a panel of five tests offered as a screen for "mental retardation," in which there are thousands of diagnostic possibilities, could be misinterpreted as an indication that "there is no genetic

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disorder," by families and nongeneticist practitioners alike. Rather, such studies should be offered in the context of a complete genetic evaluation in which all information available is assessed by an experienced clinician who focuses laboratory testing to support his or her clinical acumen.

The clinician is being presented with a continuously growing list of disorders that can be diagnosed accurately and cost-effectively with molecular-cytogenetic techniques (e.g., FISH) and direct DNA analysis. The article by Ligon et al. (1997) should serve to stimulate clinical geneticists to think about studying prospectively the cost-effectiveness and diagnostic efficiency of multiFISH panels combined with direct DNA analysis, for screening patients for disorders with overlapping phenotypic features.

References

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