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STUDY THE RELATIONSHIP BETWEEN HEMATOLOGICAL DISORDERS USING DIFFERENT TECHNIQUES LIKE FISH

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ABSTRACT

It is now more important than ever to employ fluorescence in situ hybridization (FISH) to diagnose and track disease-related chromosomal abnormalities. Ninety-two people were subjected to interphase FISH (iFISH) analysis. Five different FISH probes have been used to identify the most prevalent chromosomal rearrangements associated with haematological malignancies. A total of 83 patients were screened for BCR/ABL gene rearrangements. The iFISH patterns of BCR/ABL gene rearrangements in 37.3% of patients (31/83) ranged from 10% to 98. Although t (15; 17) (12%) and inv (16; 16) (8.3%) were present in three AML patients, t (8; 21) was not. In this study, non-random secondary chromosomal abnormalities were discovered in 6.5% of all cases. This knowledge may be used to better track the progress of therapy for patients with CML who have BCR/ABL gene rearrangements. In addition, unusual trends could have serious medical implications. The role of AML1/ETO, PML/RARA, CBFB, and p53, as well as the specific chromosomal positions and interacting genes, has to be investigated in larger patient cohorts.

KEYWORDS: - Fluorescence in Situ Hybridization, BCR/ABL, Gene Rearrangements

INTRODUCTION

Fluorescent in situ hybridization (FISH) is a powerful adjunct to conventional cytogenetics and molecular studies of the association between chromosomal abnormalities and hematologic malignancies. Due to the fact that DNA probes and FISH techniques are often not approved by the FDA, strict pre- and post-analytical conditions are required when they are utilized as reagents specific to analytes. Our mission is to inform laboratories of the various technical considerations necessary for accurate metaphase and interphase FISH testing. Technologists get comprehensive training on various probe types and the consistent evaluation of data, including coverage of both normal and pathological results. FISH is discussed in depth, including its exact nomenclature for reporting findings and its use in combination with other laboratory tests in the ongoing monitoring of sickness. This article provides detailed instructions for implementing or evaluating FISH testing programs, which, when taken in conjunction with current regulations, may lead to improved patient care. The FISH method is used in clinical laboratory research, and it involves the hybridization of a DNA probe tagged with a fluorochrome to a chromosomal target that is

visible in the body. FISH may be used on a broad variety of samples. For cytogenetic study, the "gold standard" is metaphase preparations made from cultured cells because of the clarity with which chromosome shape and signal placement can be seen. However, FISH has the advantage that it may be used to study cells that are not actively dividing. Interphase nucleus assessment from uncultured samples may be used to detect specific chromosomal rearrangements or numerical aberrations associated with haematological malignancies. Interphase analysis may also be performed on cell suspensions from bone marrow, slices of paraffin-embedded tissue, disaggregated cells from bone marrow, blood smears, and touch-preparations of cells from lymph nodes or solid tumors.

LITERATURE REVIEW

Tariq Ahmad Bhat (2017) - Fluorescence in situ hybridization (FISH) is the most accurate method for locating specific DNA sequences, detecting genetic diseases, mapping the genome, and discovering novel oncogenes or genetic defects that lead to many types of cancer. In fluorescence in situ hybridization (FISH), fluorescent reporter molecules are used to observe the annealing of DNA or RNA probes to a specific target sequence in the DNA of a sample. Recent advancements in array-based methods using comparative genomic hybridization and multicolor whole chromosome probe techniques have made it possible to screen the whole genome at once. As a powerful diagnostic and discovery tool in the fight against genetic diseases, fluorescence in situ hybridization (FISH) has revolutionized cytogenetics.

Zubair Ahmed Ratan (2017) - Fluorescence in situ hybridization (FISH), a technique for identifying macromolecules, has been heralded as a game-changer in the field of cytology. It was first developed for the purpose of locating genes on chromosomes. Because of its accuracy and versatility, FISH has been widely adopted by the biomedical research community. This visually appealing technique may be used to divide DNA analysis from chromosomal study. FISH may label cells directly or indirectly via the use of a hybridizing DNA probe. Labeling may be done directly using fluorescent nucleotides, or indirectly with reporter molecules recognized by fluorescent antibodies or other affinity molecules. FISH may be used to detect chromosomal abnormalities such as gene fusions, cell-specific chromosome losses, and deletions of small segments of chromosomes. Just two examples of how this technology is put to use in the scientific community are gene mapping and the hunt for novel oncogenes. This article provides an analysis of FISH as a medical concept, as well as its usefulness and advantages in practice.

Meenakshi A. (2015) - Over 95% of Chronic Myeloid Leukemia (CML) patients have the Philadelphia chromosome (Ph) due to a translocation between chromosomes 9 and 22 that creates the chimeric fusion gene BCR-ABL. This is a major step forward in the diagnosis and treatment of CML. The interphase and metaphase spreads of bone marrow samples may be

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examined using fluorescence in situ hybridization (FISH), a molecular cytogenetics technique, to identify BCR-ABL fusion signals. Some research suggests that white blood cells extracted from the peripheral circulation may stand in for bone marrow. Patients with Chronic Myeloid Leukemia had blood drawn from the periphery so researchers could test how quickly and precisely FISH could identify Ph positive cells. The BCR/ABL Translocation, Dual fusion probe was used in FISH on cultured peripheral blood samples from patients. Chromosomal analysis was performed using the GTG banding technique. FISH and karyotyping confirmed the presence of a reciprocal translocation t (9; 12) at (q34.1; q11.2). Our findings demonstrate that FISH is a rapid, sensitive, and quantitative method that may be used for the evaluation of CML in peripheral blood. FISH may identify disease recurrence with a minimal number of abnormal cells or little residual illness. Our data suggests that an elevated white blood cell count is associated with an increase in the number of Ph-positive cells in the blood.

Linping Hu (2014) - Many cancers have been related to recurrent genomic abnormalities, according to studies of genetic aberrations in human diseases conducted during the past two decades. Two state-of-the-art high-throughput genetic diagnostics, microarrays and next-generation sequencing, have been developed and incorporated into standard clinical practice throughout the years. Despite being a low-throughput cytogenetic test, fluorescence in situ hybridization (FISH) is becoming more important in the developing field of personalized medicine. This article discusses the most current developments in FISH application, as well as the de novo discovery and routine FISH detection of chromosomal rearrangements, amplifications, or deletions connected with the aetiology of various tumors. Recent developments in FISH methodology were also analyzed.

RESEARCH AND METHODOLOGY

The iFISH analysis was performed on 92 individuals with recognized haematological disorders, including 50 (54.34 percent) CML, 25 (27.2 percent) AML, 7 (7.6 percent) ALL, 4 (4.35 percent) CLL, and 6 (6.52 percent) MDS patients diagnosed at the Departments of Hematology. Only 59 men and 33 women were present. From the age of twenty to the age of eighty-one, they had a mean age (SD) of 50, 45 15, 19 years (Tables 1 and 2).

Slide Preparation and FISH

All patients had a 2-ml venous blood sample drawn to check for chromosomal abnormalities such as t (9;22), t (8;21), t (15;17), and/or inv (16) and/or p53 gene deletion. No incubation was employed in the harvesting or slide preparation processes. Fluorescence in situ hybridization was done on slides that had been incubated at room temperature overnight. We used the LSI BCR/ABL-ES Dual Color Translocation Probe (Vysis), LSI PML/RARA Dual Color Dual

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Fusion Translocation Probe (Vysis), LSI AML1/ETO Dual Color Dual Fusion Translocation Probe (Vysis), LSI CBFB Dual Color Break Apart Rearrangement Probe (Vysis), and LSI p53, 17p13.1, Spectrum Orange Probe (Vysis) for these experiments. To begin, slides were prepared for 5 minutes at room temperature with 2XSSC before being submerged for 30 minutes at 37 degrees Celsius in a solution containing HCl (1N), water, and pepsin A (2:200:2 v/v/v). Slides were promptly rinsed with water when the time period had expired. After that, they were treated with paraformaldehyde for 2 minutes, PBS for 2 minutes, PBS/MgCl2. 6H2O for 10 minutes, and PBS/MgCl2. 6H2O with paraformaldehyde for 10 minutes before being dehydrated with 70, 85, and 100 percent ethanol for 3 minutes each. After that, the slides were allowed to air dry. A coverslip was applied to each slide, and 10 l of each of the probe mixes was immediately applied to the slides using rubber cement. It was necessary to denaturate the slides for five minutes at 95°C before hybridizing them for an overnight period at 37°C in the ThermoBrite Denaturation/Hybridization System. 0.4XSSC/0.3% Tween 20 for 2 minutes at 73 C and 2XSSC/0.1% Tween 20 for 1 minute at room temperature were used to wash slides after the post-hybridization procedure. The slides were then left to dry in a pitch-black chamber. The next procedure was vortexing the DAPI tube and counterstaining the slides with 10 l of the dye, followed by 30 minutes at –20 C. Fluorescent microscopy was used to examine slides using red, green, and DAPI filters towards the end. A BX51 Olympus fluorescent microscope coupled with Cytovision Probe Software was used to examine interphase cells (Applied Imaging, Santa Clara, CA). A minimum of 100 interphase cells were examined for the signal patterns for each instance and probe.

DATA ANALYSIS

Researchers examined many indices [t (9; 22), t (8; 21), t(15; 17), inv (16; 16) and p53] in 92 haematological patients, including 50 (54.34%) of those with CML, 25 (27.17%) of those with AML, 4 (4.35%) of those with CLL, and 6 (6.52%) of those with MDS (Table 1).

Patients with BCR/ABL gene rearrangements were tested in a total of 83 cases. IFISH patterns for BCR/ABL gene rearrangements varied from 10% to 98% in the vast majority of patients studied, including most CML cases (25/48, 52.1%), AML (4/22, 18.2%), ALL (1/7, 14.3%), and MDS (1/6, 16.7%). (Tables 2 and 3). More than half of CML patients had a translocation of the Ph chromosome, whereas less than half had the chromosome in their DNA. Ph-positive individuals had the expected FISH signal pattern in around 96.2 percent of cases. There were four distinct iFISH patterns for BCR/ABL gene rearrangements. One fusion-der (22), one greennonrearranged 22 (29/83), and two red-der (9) with the nonrearranged chromosome 9 signals (1F2R1G) comprised the normal iFISH pattern (Pattern A). 1F1R1G and 2FG among the ph-positive patients had BCR/ABL fused gene rearrangements on chromosome 9 or the

depletion of the rearranged chromosome 9; coexistence of der(9q) and der(22q) deletions (2/25, 7.7 percent) (Figure 1).

iFISH patterns (Pattern A) were seen in 27 individuals, including 23 patients with CML, two patients with AML, one with ALL, and one with MDS (Table 3, Figure 1). Pattern B (one fusion, one red and one green signals) was detected in three individuals (3.6 percent), one of whom had CML and the other two had AML, as shown in Figure 1 and listed in Table 4. Only 2% of CML patients showed pattern C (one fusion, one red and two green signals) (Table 4, Figure 1). In our patients, the t(15;17) was found in three AML patients [3/41 (7.31 percent) examined patients for PML/RARA]; C28, C47, and C67, with the rates of 11%; 79%; and 86%, respectively (Tables 2 and 3). This treatment was tested on 19 people. Only 12/100 interphase cells from 12 different AML patients (C11) revealed this inversion (Tables 2 and 3, Figures 2(c) and (d)). Seven individuals with CML, AML, and CLL were examined for p53 gene deletion. C54, the only CML patient tested positive, had a 10% chance of remission. The p53 gene was not deleted in any of the other cases (Tables 2 and 3).

Table 1. The distribution of hematological cancers in the present study.

Hematological disorder	**n (%)**	
Chronic myeloid leukemia (CML)	50 (54.34)	
Acute myeloid leukemia (AML)	25 (27.17)	
Acute lymphoblastic leukemia (ALL)	7	(7.6)
Chronic lymphoblastic leukemia (CLL)	4	(4.35)
Myelodysplastic syndrome (MDS)	6	(6.52)
Total	**92**	

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Table 2. The demographic information and iFISH results of the study population.

Case No	Age	Sex	Disease	*BCR/ ABL* [t (9; 22)] %	*AML1/ ETO* [t (8; 21)] %	*PML/ RARA* [t (15; 17)] %	*CBFB* [inv (16; 16)] %	*P53* [del (p13.1)] %	The other chromosomal aberrations (%)
C1	42	M	CML	**10**	–	–	–	–	–
C2	64	M	CML	**21**	–	–	–	–	–
C3	49	F	CML	**77**	–	–	–	–	–
C4	38	F	CML	**12**	–	–	–	–	–
C5	57	M	CML	**50**	–	–	–	–	–
C6	70	F	AML	–	–	0	–	–	–
C7	58	F	CML	**80**	–	–	–	–	–
C8	64	M	CML	0	–	–	–	–	–
C9	62	M	CML	**84**	–	–	–	–	–
C10	44	F	CML	0	–	–	–	–	–
C11	70	M	AML	3	7	4	**12**	–	–
C12	49	M	CML	**86**	5	9	5	–	–
C13	58	F	CML	7	5	5	8	–	–
C14	77	M	MDS	**11**	2	3	5	–	–
C15	70	M	AML	0	3	3	8	–	–
C16	68	F	ALL	6	3	6	3	–	–
C17	45	M	CML	**88**	–	–	–	–	–
C18	29	M	CML	**88**	–	–	–	–	–
C19	46	F	CML	**37**	–	–	–	–	–
C20	30	M	CML	**26**	–	–	–	–	–
C21	37	M	CML	**89**	2	5	1	–	–
C22	44	F	ALL	5	2	7	5	–	–
C23	70	M	CML	0	–	–	–	–	–
C24	41	M	CML	0	–	–	–	–	–
C25	37	F	AML	8	2	4	1	–	–
C26	35	F	AML	–	2	5	2	–	–
C27	43	M	AML	**12**	8	5	3	–	–
C28	44	F	AML	**55**	2	**11**	3	–	–
C29	52	M	AML	**10**	2	4	2	–	–
C30	59	M	ALL	**21**	–	–	–	–	–

C31	81	F	CML	6	1	6	0	–	–
C32	38	F	CML	**97**	–	–	–	–	–
C33	39	F	MDS	9	0	3	–	–	–
C34	36	M	ALL	6	4	4	–	–	–
C35	74	F	AML	5	3	8	–	–	**Monosomy 9 (70%)**
C36	21	M	AML	**11**	–	9	–	–	–
C37	75	M	AML	6	5	9	–	–	–
C38	54	M	MDS	5	1	6	–	–	**Trisomy 8 (16%)**
C39	70	F	CML	6	–	–	–	–	–
C40	20	F	CML	0	2	0	–	–	–
C41	60	M	CML	**86**	0	0	–	–	–
C42	77	M	CML	0	–	–	–	–	–
C43	59	M	MDS	7	–	–	–	–	–
C44	51	M	CML	**88**	–	–	–	–	–
C45	60	F	CML	**93**	–	–	–	–	–
C46	46	M	CLL	–	–	–	–	–	–
C47	55	M	AML	2	1	**79**	–	–	–
C48	70	M	MDS	0	0	1	–	–	–
							–	–	**Monosomy 17 (25%)**
C49	61	F	AML	3	0	5			**Trisomy 8 and**
									monosomy 21 (37%)
C50	76	M	CML	8	–	–	–	–	–
C51	56	M	CLL	–	–	–	–	0	–
C52	70	F	CML	1	–	–	–	–	–
C53	70	F	AML	2	–	–	–	0	–
C54	60	M	CML	–	–	–	–	**10**	–
C55	63	F	CML	**96**	–	–	–	–	–
C56	56	M	CML	**6**	–	–	–	–	–
C57	56	M	CML	**5**	–	–	–	–	–
C58	43	M	CML	**3**	–	–	–	–	–
C59	59	M	CML	**86**	–	–	–	–	–
C60	69	M	CML	**7**	–	–	–	–	–
C61	51	M	CML	**–**	–	–	–	0	–
C62	23	F	ALL	**7**	–	–	–	–	–
C63	40	M	AML	**6**	–	2	–	–	–
C64	35	F	MDS	**6**	0	4	–	–	–
C65	53	M	AML	**0**	0	8	0	–	–

C66	69	F	AML	**–**	1	4	2	–	Trisomy 21 (85%)
C67	35	F	AML	**4**	-	86	0	–	Trisomy 8 (3%)
C68	33	M	AML	**3**	4	5	–	–	–
C69	54	M	AML	**2**	-	6	0	–	–
C70	54	M	AML	**0**	0	3	–	–	–
C71	47	M	AML	**9**	0	4	–	–	Trisomy 8 (98%)
C72	64	M	AML	**4**	0	4	–	–	–
C73	42	M	AML	**0**	–	0	0	–	–
C74	30	F	CML	**85**	–	–		–	–
C75	54	M	CML	**1**	0	3	–	–	–
								–	Tetrasomies 8 and 21
C76	38	F	ALL	**4**	0	0	–		
									(55%)
C77	48	M	AML	**5**	4	0	–	–	Trisomy 8 (89%)
C78	23	M	CML	**4**	–	–	–	–	–
C79	46	F	CML	**0**	–	–	–	–	–
C80	60	M	CLL	**–**	–	–	–	0	–
C81	49	M	CML	**45**	–	–	–	–	–
C82	58	M	CML	**93**	–	–	–	–	–
C83	54	F	CML	**6**	–	–	–	–	–
C84	25	F	CML	**5**	–	–	–	–	–
C85	47	M	CML	**8**	–	–	–	–	–
C86	46	M	CLL	**–**	–	–	–	4	–
C87	28	M	CML	**20**	–	–	–	–	–
C88	41	M	CML	**5**	–	–	–	–	–
C89	26	M	CML	**90**	–	–	–	–	–
C90	25	M	CML	**98**	–	–	–	–	–
C91	22	F	ALL	**3**	0	4	–	–	–
C92	44	M	CML	**0**	–	–	–	–	–

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Table 3. The distribution of the patients according to the results of BCR/ABL, AML/ETO, PML/RARA, CBFB and *P*53.

			% (Positive results/total number of patients)				
Hematologic disorder	**BCR/ABL [t(9; 22)]**		**AML/ETO**		**PML/RARA**	**CBFB [inv(16; 16)]**	**p53 [del(p13.1)]**
			[t(8; 21)]		**[t(15; 17)]**		
CML	52.1	(25/48)	0	(0/7)	0 (0/7)	0 (0/4)	50 (1/2)
AML	18.2	(4/22)	0	(0/18)	12.5 (3/24)	8.3 (1/12)	0 (0/1)
ALL	14.3	(1/7)	0	(0/5)	0 (0/5)	0 (0/2)	–
MDS	16.7	(1/6)	0	(0/5)	0 (0/5)	0 (0/1)	–
CLL	–		–		–	–	0 (0/4)
Total	83		35		41	19	7

Table 4. Distribution of typical and atypical iFISH patterns with the ES probe in BCR/ABL+ leukemias studied at diagnosis.

iFISH pattern with		**Chromosomal localization of signals**				**Number of Ph positive cases (%)**		
***BCR/ABL* ES probe**	F	R	G		CML	AML	ALL	MDS
					(*n* = 25)	(*n* = 4)	(*n* = 1)	(*n* = 1)
A: 1F 2R 1G	1F(Ph)	2R (9)	1G (22)		**23 (92%)**	**2 (50%)**	1 (100%)	1 (100%)
B: 1F 1R 1G	1F(Ph)	1R (9)	1G (22)	1 (4%)		**2 (50%)**	–	–
C: 1F 1R 2G	1F(Ph)	1R (9)	2G (22,22)	1 (4%)		–	–	–

F: fusion, R: red, G: green, A: Representative schemes of nuclei carrying typical *BCR/ABL*; B and C: atypical *BCR/ABL* fused gene rearrangements on chromosome 9 or 9q deletion of the rearranged chromosome 9; coexistence of der(9q) and der(22q) deletions.

8/92 of our patients, on the other hand, had numerical chromosomal deficits or increases. In C35, a 74-year-old AML patient, 70 out of 100 cells were found to have monosomy 9. Trisomy 8 cells were found in 16 percent of MDS cells, 3 percent of AML cells, 98% of AML cells, and 89% of AML cells from the C38, C67, C71, and C77 cell lines. Additionally, the research discovered trisomy 21 in C66 (AML) (85%), tetrasomies 8 and 21 in C76 (ALL) (55%), and trisomy 8 in combination with monosomy 21 (37%) and monosomy 17 (25%) in C49 (AML) (Table 2, Figure 3).

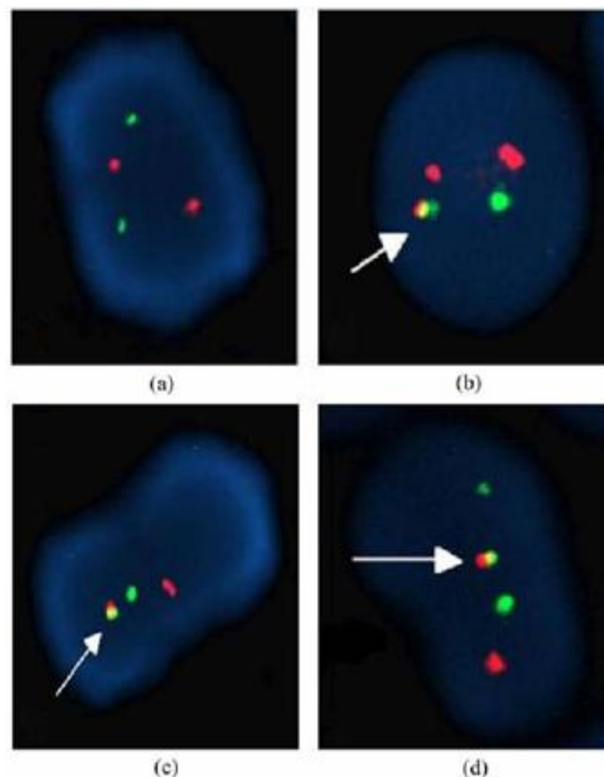

Figure 1. Different interphase FISH (iFISH) patterns found with the LSI *BCR/ABL* ES Dual Color Translocation probe (a)Normal nuclei, (b) 1F 1G 2R pattern (pattern A), (c) 1F 1G 1R pattern (pattern B), (d) 1F 2G 1R pattern (pattern C).

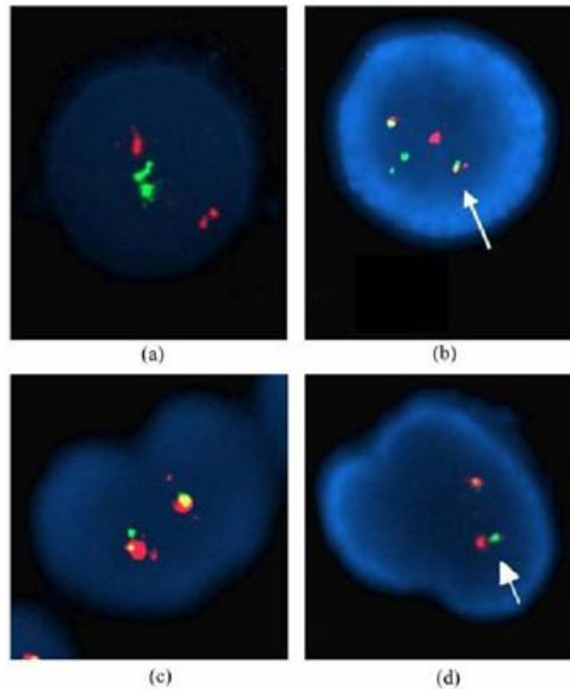

Figure 2. Interphase nuclei showing normal pattern and t (15;17) found with LSI *PML/RARA* Dual Color Dual Fusion Translocation Probe (a-b), normal pattern and inv (16) found with LSI *CBFB* Dual Color Break Apart Rearrangement Probe (c-d).

CONCLUSION

For many neoplastic illnesses, including those of the blood and other tissues, FISH has become an essential tool for diagnosis and follow-up. Because of this, the validation of the FISH probes and technical procedures, as well as the training of the people who will be doing the testing, must be carried out in a fairly thorough fashion. It also calls for a means of providing the results that is both comprehensive and easy to understand. As the number of important loci involved in neoplastic chromosomal rearrangements or numeric aberrations rises, so too will the number of FISH probes and unique probe sets. FISH has emerged as a crucial diagnostic method due to its ability to detect and characterize chromosomal abnormalities at an early stage in the disease process and its consistency in monitoring patients' responses to therapy and eventual recoveries.

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