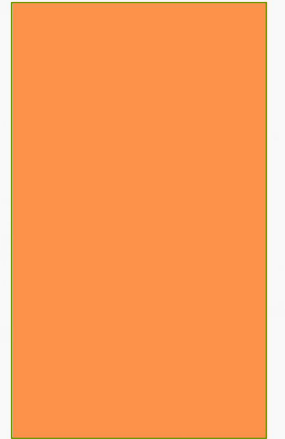


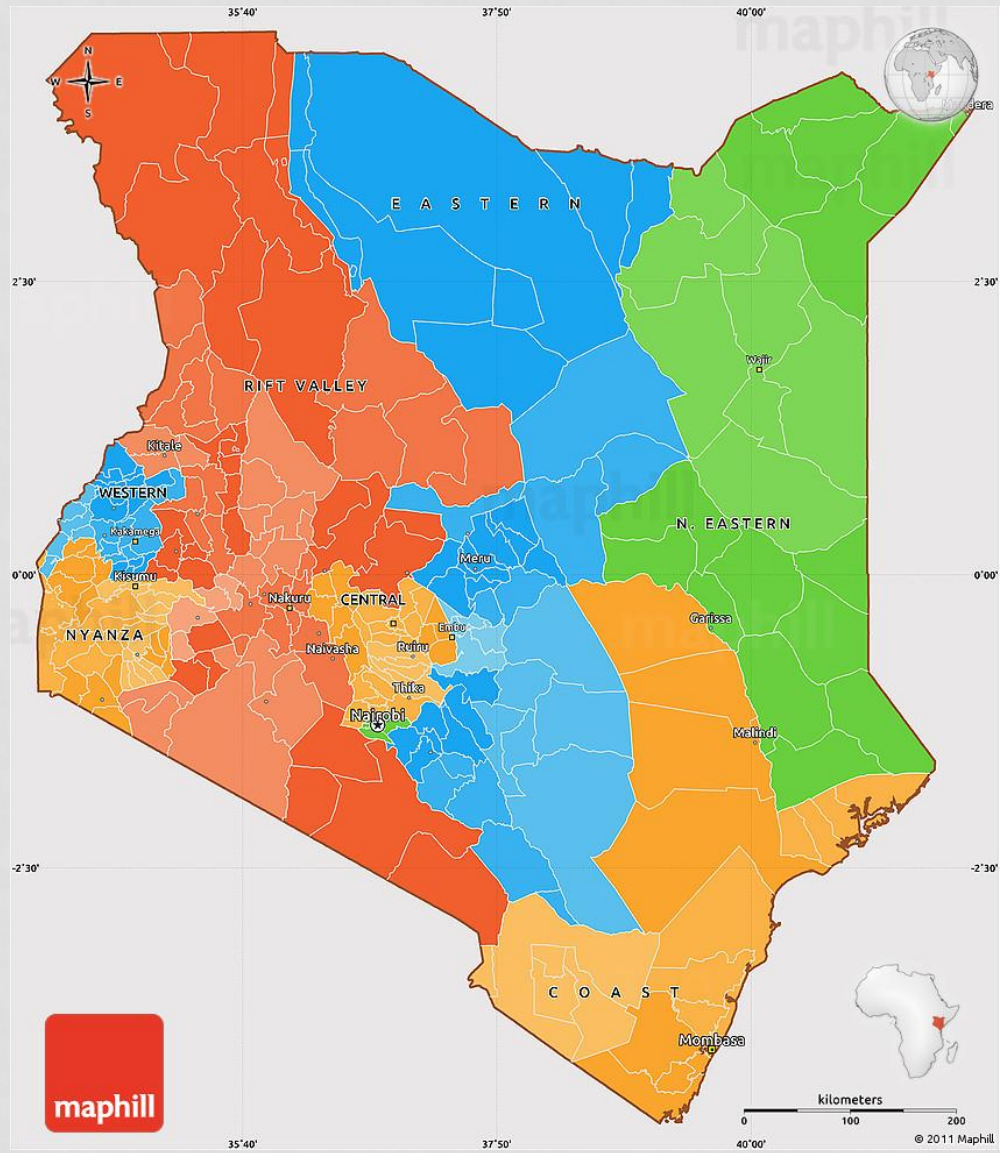
CML MANAGEMENT IN EMERGING COUNTRIES: ACCESS TO MONITORING

N.A. OTHIENO-ABINYA
UNIVERSITY OF NAIROBI,
NAIROBI-KENYA









KENYA COUNTRY PROFILE

- Location
 - East Africa
- Total population
 - 50,950,879
- Gross national income per capita (PPP International\$) (2016)
 - 3230 US \$
- Total expenditure on health per capita (Intl \$, year) (2014)
 - 77.7 US \$
- Total expenditure on health as a GDP (WHO Stats) (2014)
 - 6.8%
- Life expectancy at birth M/F (2015)
 - 61/66 (2015)

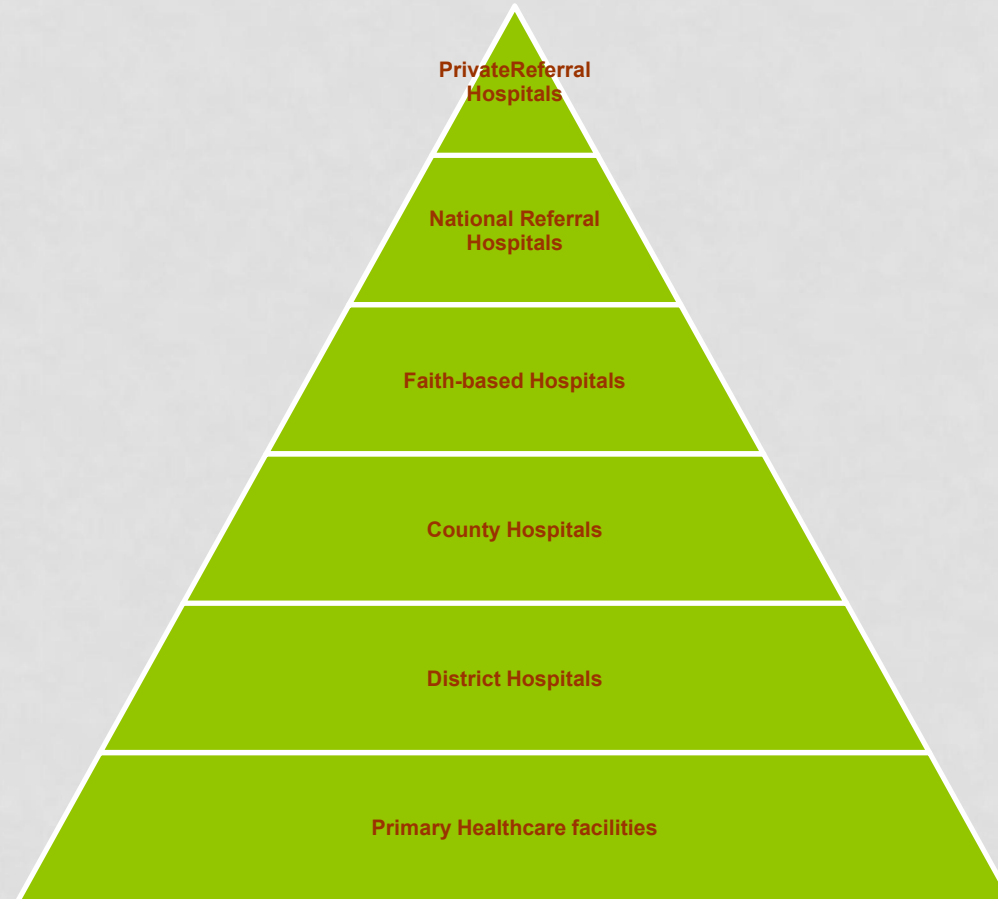
STRUCTURE OF HEALTH SYSTEM

Health care providers:

- ❖ Hospitals
 - ❖ Public hospitals
 - ❖ Faith based/private not for profit
 - ❖ Private not for profit
 - ❖ Private for profit

- ❖ HMOs

- ❖ Universities
 - ❖ Nairobi
 - ❖ Moi
 - ❖ Kenyatta
 - ❖ Maseno



NUMBER OF HOSPITALS/INSTITUTIONS THAT PROVIDE CANCER CARE IN KENYA

Type of service	Number of sites	Location
1. Comprehensive cancer centres	• 3	Nairobi
2. Radiation oncology centres	• 3	Nairobi, Eldoret
3. Medical oncology and haematology centres	• 3	Eldoret, Mombasa, Kisumu
• 3. Diagnostic centres	• Numerous	In urban areas
• 4. Surgical oncology	• -	
• 5. Palliative services	• Many	

CANCER PROFESSIONALS REGISTERED IN KENYA

Category	Number
• Medical oncology	7
• Clinical oncology	4
• Radiation oncology	5
• Paediatric oncology	1
• Haematology	3
• Surgical oncology	3
• Oncology nursing	
• Radiophysicists	
• Radiotherapists	
• Urologists	

FIRST GROUP OF MEDICAL ONCOLOGY FELLOWS AT THE GIPAP CLINIC



CHRONIC MYELOGENOUS LEUKAEMIA: MASSIVE SPLENOMEGALY



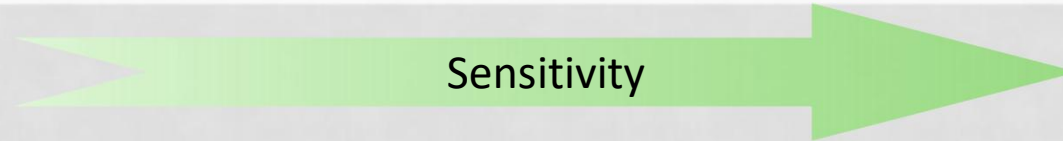
PRESENTING COMPLAINTS AMONG PATIENTS SEEN AT THE HONC GIPAP CLINIC- 380 PATIENTS(450 SYMPTOMS ANALYZED)

• Symptom	• Number	%
• Abdominal complaints	207	46
• Nonspecific systemic symptoms	118	26.2
• Subcutaneous nodules	29	6.4
• Joint pains	26	5.8
• Leg swellings	24	5.3
• bleeding tendency	14	3.1
• Impaired hearing	8	1.8
• Impaired vision	6	1.3
• priapism 6 (1.3%), tinnitus 2 (0.4%).	6	1.3
• Tinnitus	2	0.4

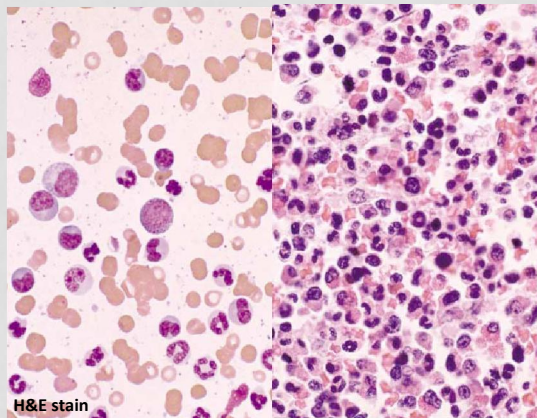
SYMPTOMS AND FINDINGS AMONG 81 PATIENTS WITH CML AT THE UNIVERSITY OF UTAH

SYMPTOM	% OF PTS	FINDINGS	% OF PTS
• Fatigue	83	• Splenomegaly	95
• Weight loss	61	• Hepatomegaly	48
• Abdominal fullness	38	• Sternal tenderness	78
• Easy bruising/bleeding	35	• Purpura	27
• Abdominal pain	33	• Retinal haemorrhage	21
		• Fever	11
		• Palpable lymph nodes	64
		• Palpable lymph nodes Exceeding 1 cm diameter	8

DIAGNOSTICS IN CML



Hematologic

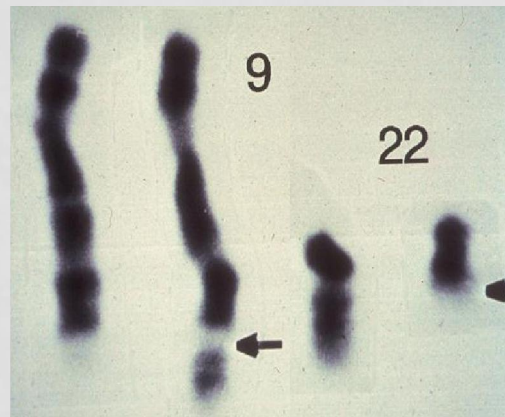


Peripheral Blood
(with myeloid cells)

Bone Marrow
(myeloid hyperplasia)

Cytogenetic

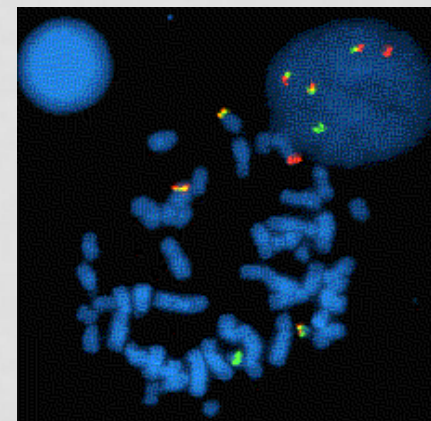
Karyotype (Ph chromosome)



Chromosomal translocation
 $t(9;22)(q34;q11)$

FISH

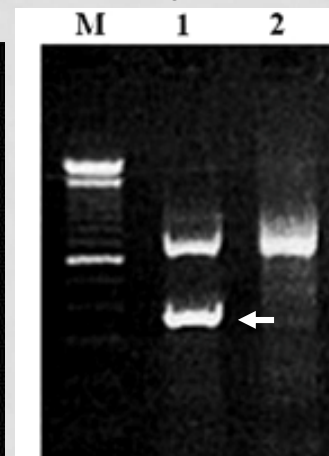
(BCR-ABL fusion)



Abnormal BCR-ABL
Red= BCR
Green= ABL
Yellow=Fusion

Molecular


PCR



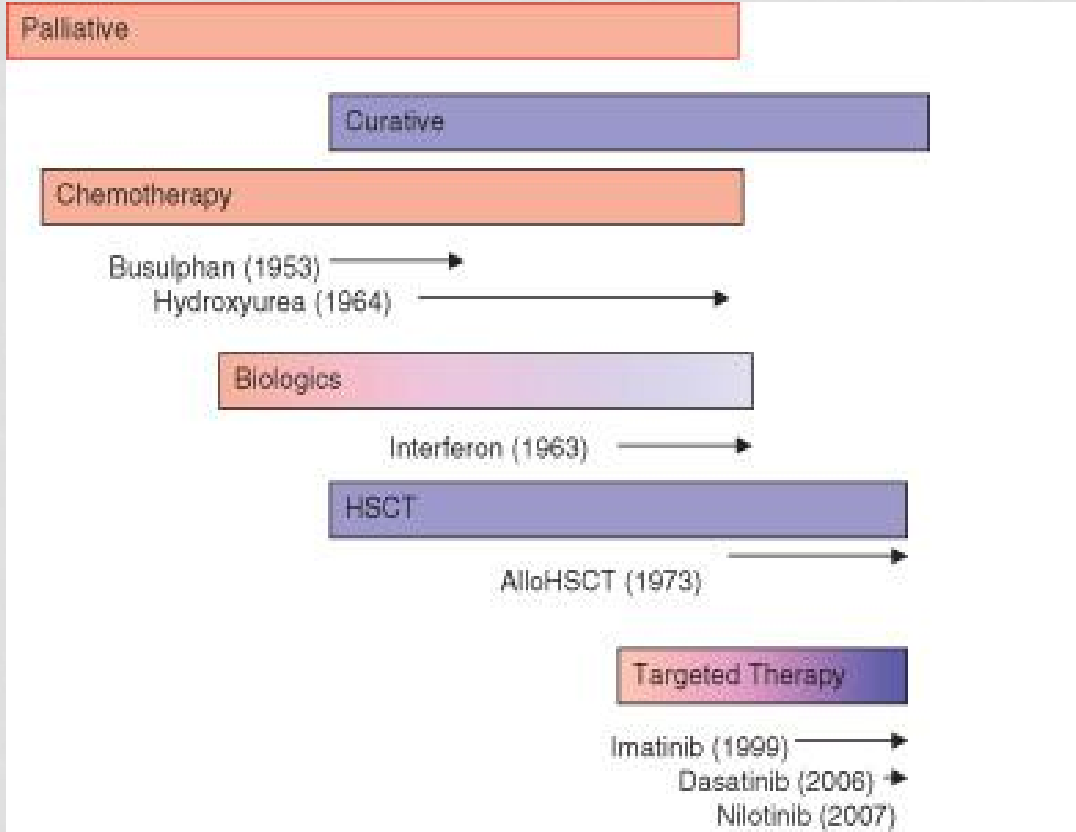
Abnormal BCR-ABL
Lane 1= BCR-ABL+ sample
Lane 2= BCR-ABL- sample

Clinical Course: Phases of CML

Chronic phase	Advanced phases	
	Accelerated phase	Blast crisis
Median 5–6 years stabilization	Median duration 6–9 months	Median survival 3–6 months



HISTORY OF THERAPY



HISTORY OF CML TREATMENT IN KENYA

1975

1985

1995

2005

2015

Busulfan.....

Hydroxycarbamide.....

Imatinib mesylate.....

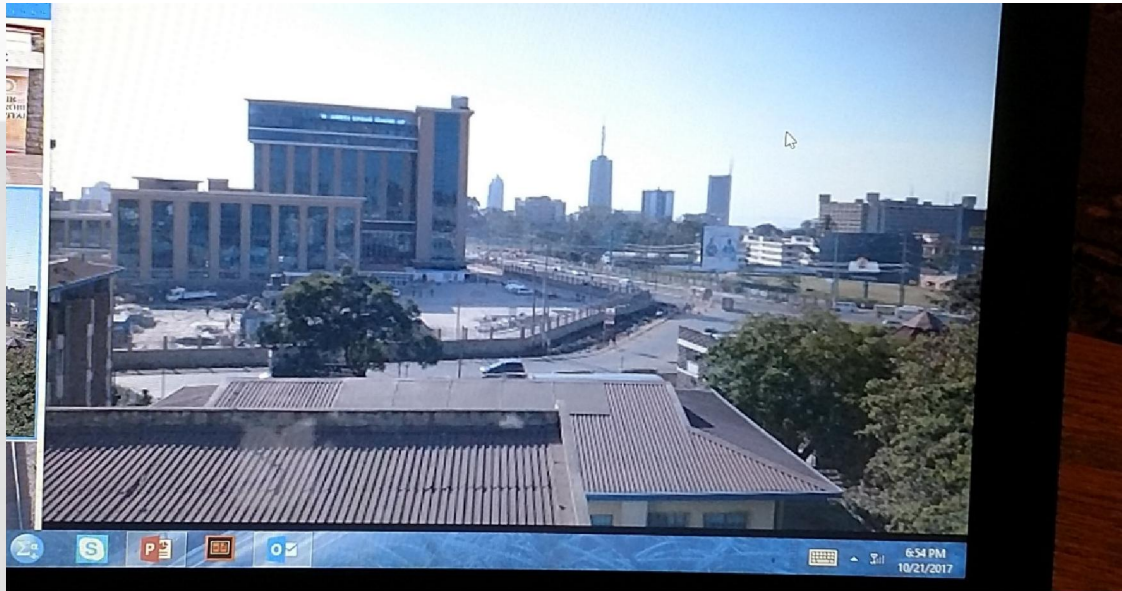
Second and.....
third
generation
TKIs

PATIENTS WAITING FOR RADIOTHERAPY AT A PUBLIC HOSPITAL.



NAIROBI - DISPARITIES: SAME CITY, DIFFERENT OPPORTUNITIES





BIG BROTHER CANNOT BE IGNORED

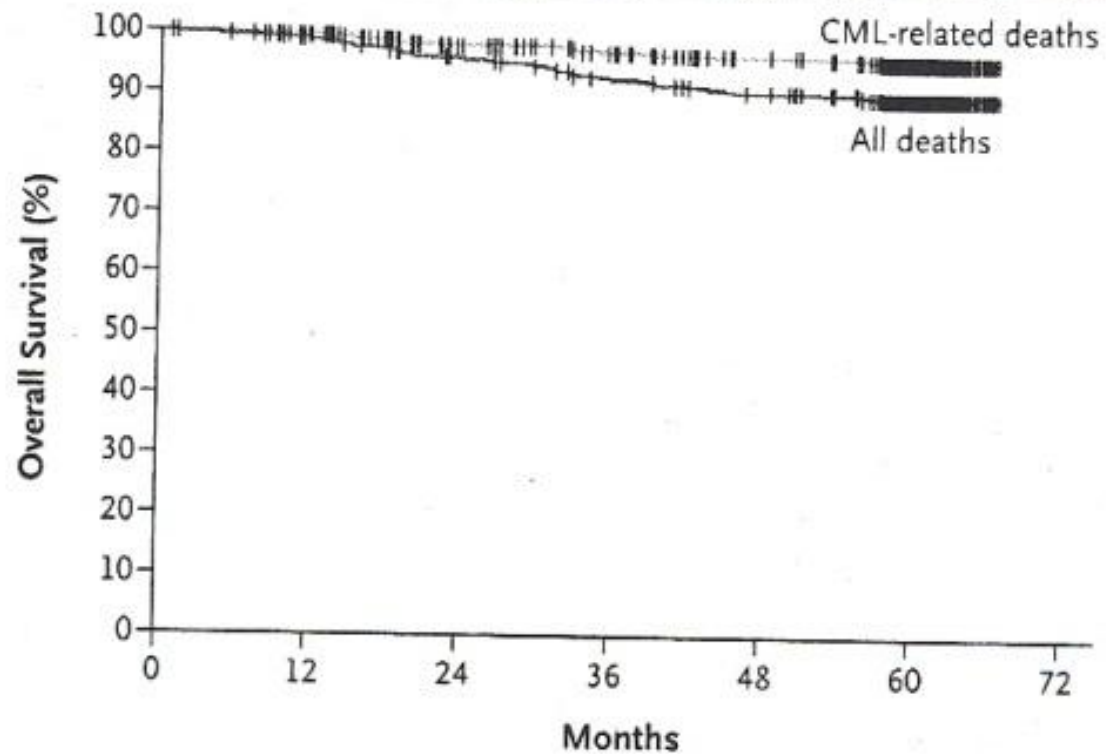


THERE IS HOPE

- With currently available therapies, however, median survival might extend to **30 years or more** and some patients may never transform and may never die of their leukemia.

BUT

- Although most patients achieve a complete cytogenetic response, the majority of these patients have **detectable leukemia as analyzed by BCR-ABL RT-PCR**.
- Most have persistent disease at the molecular level and most have relapsed if imatinib was discontinued.



No. of Deaths						
Related to CML		3	11	16	19	23
All deaths		6	22	41	52	57
No. at Risk						
Related to CML		536	498	474	450	322
All deaths		542	518	492	475	333

Figure 4. Overall Survival among Patients Treated with Imatinib Based on an Intention-to-Treat Analysis.

MILESTONES OF TREATMENT

Complete Hem response	3 months
Major cytogenetic response ($<35\%$ Ph+ metaphases)	6 months
Complete cytogenetic response	12 months
Major molecular response	18 months

Table 1. Definitions of response.

Level of Response	Definition
Complete hematologic response (CHR)	Normal full blood count and white cell differential count, no evidence of extramedullary disease
Minimal cytogenetic response	66%-95% Ph-positive metaphases*
Minor cytogenetic response	36%-65% Ph-positive metaphases*
Partial cytogenetic response	1%-35% Ph-positive metaphases*
Complete cytogenetic response (CCR)	0% Ph-positive metaphases*
Major cytogenetic response (MCR)	0%-35% Ph-positive metaphases*
Major molecular response (MMR)	≥ 3 -log reduction of BCR-ABL mRNA
Complete molecular response (CMR)	Negativity by RT-PCR

*Based on the analysis of at least 20 metaphases.

CURRENT MOST DESIRABLE GOAL: DEEP MOLECULAR RESPONSE

Description	BCR-ABL Level %
• MR4	• <0.01
• MR4.5	• <0.0032
• MR5	• <0.001

MONITORING OF CML RESPONSE IN KENYA

1975

1985

1995

2005

2015

Haemogram.....

Bone marrow.....

PCR..

RESISTANT DISEASE

Primary Resistance

Failure to achieve complete heme response at 3 to 6 months

Failure to achieve major cytogenetic response at 12 months (<35% Ph+ metaphases)

Failure to achieve complete cytogenetic response at 18 months

Secondary Resistance: loss of MMR or CCyR

4% per year suffer loss or progression

	Monitoring				Total
Purpose of test Laboratory	Diagnosis No (%)	1	2	3	No (%)
Lancet Kenya	36(52.9)	7	0	1	44(47.3)
Nairobi Hospital	17(25)	10	3	2	32(34.4)
Aga Khan Hospital	6(8.8)	0	0	0	6(6.5)
Medanta	3(4.4)	0	0	0	3(3.2)
Medipath	2(2.9)	1	0	0	3(3.2)
KNH	1(1.5)	0	0	0	1(1.1)
Star Biotech	1(1.5)	0	0	0	1(1.1)
Metropolitan	1(1.5)	0	1	0	2(2.2)
Pathcare	1(1.5)	0	0	0	1(1.1)
Total	68(100)	18	4	3	93(100)

Random sample of 93 patients treated at HOC

WHAT IS REQUIRED FOR EFFECTIVE MONITORING?

- 1. Well trained PCR personnel on open PCR system
- 2. Good work habits to avoid contamination
- 3. Closed PCR system is more reliable
- 4. Setting up laboratory space correctly and cultivating habits that prevent cross-contamination is vital

LANCET KENYA

LANCET KENYA (PLK)
Key to diagnostic excellence
Macharia ya Ruaha
Email : info@lancet.co.ke
Website : www.lancet.co.ke

8th Floor - 5th Avenue Building
Tel : +254 20 493-1000

PATHOLOGY LAB REPORT

For Doctor
KENYATTA NATIONAL HOSPITAL (U)
HOSPITAL ROAD, KENYATTA
TEL: +254 20 2726300
XXXX NAIROBI

Other Doctors
Copy : SMS PATIENT REPORT ALERT

Patient : IBRAHIM KIMILU
Doctors Ref: 1806135
Age/Sex/DOB: 30 / M /
Id Num : NOT AVAILABLE

Guarantor : MR I KIMILU
MedAid : KE LOW N
Tel : (W) NOT AVAILABLE

Lab Ref : 732807460
MRI No. : K000790123
Spec # : 0418:DG00001U

Collection Date : 18/04/16 1040
Received Date : 18/04/16 1055
FINAL Report Date : 22/04/16 1614

Requested : .. PCR BCR/ABL FUSION
P.C.R GENETIC DISEASES

Quantitation of BCR-ABL fusion transcripts.
(Cepheid Xpert BCR-ABL Monitor)

> BCR-ABL 9-22 ** POSITIVE
> IS ratio BCR-ABL/ABL 85 %
> COMMENT
The GeneXpert BCR/ABL Assay detects BCR-ABL chromosomal translocation. It detects p210 (b2a2 and B3a2) transcript in peripheral blood lymphocytes using real-time PCR. The

LABORATORY
XXXX NAIROBI

Patient : PAUL NGANGA MBUI
Doctors Ref: NOT AVAILABLE
Age/Sex/DOB: 30 / M /
Id Num : 25108290

Guarantor : MR P MBUI
MedAid : JUBILEE 2012050/00
Tel : (W) NOT AVAILABLE

Lab Ref : 729005818
MRI No. : K001084025
Spec # : 0828:DG00001L


Collection Date : 28/08/17 10
Received Date : 28/08/17 11
FINAL Report Date : 29/08/17 16

Requested : .. PCR BCR/ABL FUSION
ADDITIONAL INFO EMPLOYER NAME: KENYA FILM CLASSIFICATION
P.C.R GENETIC DISEASES

Quantitation of BCR-ABL fusion transcripts.
(Cepheid Xpert BCR-ABL Monitor)

> BCR-ABL 9-22 ** POSITIVE
> IS ratio BCR-ABL/ABL 0.0033 %
> COMMENT
The GeneXpert BCR/ABL Assay detects BCR-ABL chromosomal translocation. It detects p210 (b2a2 and B3a2) transcript in peripheral blood lymphocytes using real-time PCR. The presence of this translocation is used in the diagnosis and therapeutic monitoring of chronic myeloid leukaemia (CML).

THE NAIROBI HOSPITAL


P. O BOX 30026, NAIROBI
TEL: 2845700 HAX: 2845705
DEPARTMENT OF PATHOLOGY

Name: PAUL MBUI
Sex: MALE
Ward: OPD
Acc no: 67263

DR MD MAINA
NH NO 2068641
RAPHAEL

Age 30 YRS

GENE EXPERT FOR PHILADELPHIA CHROMOSOME

Test principle : Real Time PCR
Specimen : Blood.

RESULT
BCR-ABL was detected at detection level of 38% (IS)

Clinical background

- BCR-ABL transcript quantification is expressed as a % of the control ABL.
- The sample showing amplification curve for both BCR/ABL transcript are considered as positive for the test and are reported as a % expression

REFERRED BY : DR.KNH
AGE : 23 YEARS
LOCATION : OPD
ADM NO :
GENDER :
BILL DATE : 27
SAMPLE COLL DATE : 27

PHILADELPHIA CHROMOSOME STUDIES

Test	Result
------	--------

Comments : REPORT

FISH PROCEDURE- PRENATAL
FISH PROCEDURE - CELL CUL

FISH ANALYSIS FOR PHILADELPHIA CHROMOSOME
Uncultured leucocytes were analysed using FISH and locus specific DNA probes for a part of the abloncogenes, on chromosome 9, to the bcr ("breakage cluster region") on chromosome 22. The Philadelphia chromosome originates from this translocation.

RESULT:
Philadelphia positive(fusion positive) 95.4% (250 cells)
Philadelphia negative(fusion negative) 4.6%(10 cells)

referral laboratory

AGAKHAN OTHER

PATIENT NAME : MR EMMANUEL OCHIENG SAMPLE RECEIVED DATE : 27/06/2014 01:12:21PM
 PATIENT AGE : YEARS REPORT PRINTED ON : 11-Jul-2014 01:05:29 PM
 PATIENT GENDER : MALE SOURCE LOC. : MAIN LABORATORY
 PRES. DOCTOR : A. N. OTHER DOCTOR LOCATION : OPD
 REFERRED BY : DR. AKH KISUMU REGISTRATION TYPE : External
 REFERRAL LOC. : AKH KISUMU. EXT PRESC. DOCTOR :

Sample Type :

Test	Result
Interpretation :	INTERPRETATION OF RESULTS
	NOT DETECTED (NEGATIVE) A negative result for bcr-abl transcript may indicate a negative diagnostic sample or, in a patient on treatment, a complete molecular response.
	POSITIVE A positive result indicates BCR-ABL transcript has been detected.
	PERCENT For positive results, a percent is given, determined from the ratio of BCR/ABL to ABL. A ten-fold reduction in percent (eg. 20% to 2%) is a one log improvement. This result is standardized to the European LeukemiaNet consortium guidelines.
	Criteria for molecular response

CLIENT CODE : C000029782
 CLIENT'S NAME AND ADDRESS :
 MEDIPATH LABORATORIES KENYA LIMITED
 2ND FLOOR, MAYFAIR INSURANCE CENTRE, NEXT TO UPPER HILL
 MEDICAL CENTRE
 RALPH BUNCHE ROAD,
 NAIROBI 4149001000
 KENYA
 0025-733-743792

SRL LIMITED
 PRIME SQUARE BUILDING, PLOT NO 1, GAIWADI IN
 ESTATE, S.V. ROAD, GOREGAON (W)
 Mumbai, 400062
 MAHARASHTRA, INDIA
 Tel : 022-6780 1177/1-800-222-660, Fax : 022-
 Email : srl.mumbai@srl.in

PATIENT NAME : DENNIS NZIVO
 AGE : 17 Years SEX : Male DATE OF BIRTH :
 ACCESSION NO : 0002ME037974
 DRAWN : 11/05/2013 00:00 RECEIVED : 13/05/2013 08:41 REPORTED : 15/05/2013
 REFERRING DOCTOR : DR. COPTIC
 CLINICAL INFORMATION :
 BLOOD SAMPLE

Test Report Status	Final	Results
MOLECULAR BIOLOGY		
BCR/ABL - QUANTITATIVE		BLOOD
SPECIMEN SOURCE		68.40
METHOD - REAL TIME PCR		
BCR/ABL TRANSLOCATION RATIO		
METHOD - REAL TIME PCR		

Test Method(s)
 BCR-ABL - QUANTITATIVE: Real Time Reverse Transcriptase Polymerase Chain Reaction

OTHER LAB

- Medanta

- Mid East

medanta
AfriCare
MEWA LAB IPD CORPORATES
MOMBASA
Mombasa
KENYA

NAME: **SOLOMON KINYANJUI** AGE: 43 Years SEX: Male
 ACCESSION NO: **5011FA001443** PATIENT CD: **SOLOM1801745011**
 COLLECTED ON: REGISTERED ON: **18/01/2017 14:30** REPORTED ON:
 REFERRED BY: **DR. NDEGWA**

TYPE OF TRANSLOCATION
BCR-ABL- GENE REARRANGEMENT , PCR QUANTITATIVE (Real Time PCR)

BCR-ABL gene rearrangement	70.760	%
Type of Translocation	Major	
BCR-ABL International Scale Normalized copy number	44.296	

Interpretation

IS-NCN	REMARKS
< 0.05	Major Molecular Response
0.05 - 0.15	Gray zone around major molecular response cutoff, inc
>0.15	No Major molecular response

Meditest Diagnostic Services Ltd
Pathology: The Science behind the cure

C000000512-KENYA - MEDITEST DIAGNOSTIC SERVICES LIMITED

NAME: **JUMA ABDALLA** AGE: 55 Years SEX: Male
 PATIENT CD: **JUMAM2606621** File No:
 LAB REF NO.: **170053921** ACCESSION NO: **0001FF002696**
 COLLECTED ON: 23/06/2017 00:00 REGISTERED ON: 26/06/2017 13:11 REPORTED ON: 04/07/2017 16:32
 Report Status: **Final** REFERRED BY: **SELF**

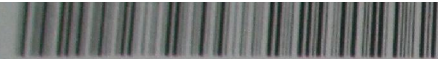
Tests	Results	Biological Reference Range	Units
# BCR/ABL, QUALITATIVE, MBCR-CML	DETECTED	NOT DETECTED	
BCR/ABL, QUALITATIVE, MBCR-CML			
METHOD: PCR			
Specimen: EDTA WHOLE BLOOD			

End Of Report

This Test(s) were performed at our affiliated Labs.

Arjill
Dr. V S Aiyer MD, FRC Path (UK)
Specialist Clinical Pathologist
DHA-P-0133157

Varsha
Dr. Varsha Pradeep Ingale
Specialist Clinical Pathology
DHA-P-0185731



2017/MB/001254

Date of Report

3/6/17

PATIENT BIODATA & INFORMATION

Patient ID	Damacline Kerubo	Specimen	Whole Blood
Gender	F	Age	31
		Date of Receipt	29/6/17
Referred By	Prof N A Othieno-Abinya		

TEST RESULTS

Test Requested	<i>BCR-ABL T315I Mutation Study</i>
Result	Not Detected
Analysis	

IN CONCLUSION

- CML management in Kenya today is mainly based on imatinib.
- Those failing therapy are put on second- and third-generation TKIs.
- Monitoring of therapy is still mainly based on haematological parameters.
- Cytogenetics and FISH monitoring are not carried out.
- BCR-ABL qPCR monitoring is becoming popular, but without standardization, and various laboratories, some even with dubious credentials are purporting to carry out the test.
- Cost is a major deterrent to appropriate monitoring.
- The situation in most African countries could be worse.

