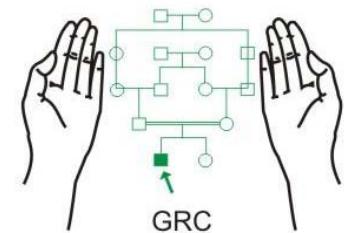


Molecular Aspects of Leukaemia & Lymphoma

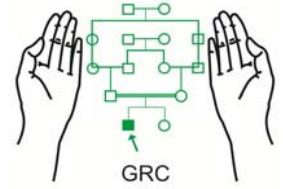
Maj Gen (R) Suhaib Ahmed, HI (M)
MBBS; MCPS; FCPS (Pak); PhD (London)

Genetics Resource Centre (GRC)

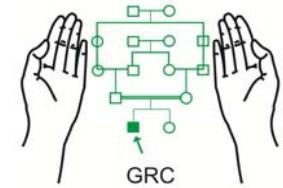


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Prognostic Stratification



- Morphology
- Immunophenotyping
- Genetic Analysis
 - Cytogenetic
 - Molecular Genetic



WHO Classification of AML

Acute myeloid leukemia with recurrent genetic abnormalities

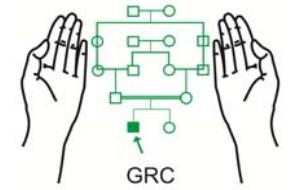
- AML with t(8;21)(q22;q22); (*RUNX1;RUNX1T1*)
- AML with inv(16)(p13.1q22) or t((16;16)(p13.1;q22); (*CBFB-MYH11*)
- APL with t(15;17)(q22;q12); (*PML-RARA*)
- AML with t(9;11)(p22;q23); (*MLLT3-MLL*)
- AML with t(6;9)(p23;q34); (*DEK-NUP214*)
- AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); (*RPN1-EVT1*)
- AML (megakaryoblastic) with t(1;22)(p13;q13); (*RBML5-MKL1*)
- Provisional entity: AML with mutated NPM1
- Provisional entity: AML with mutated CEBPA

Acute myeloid leukemia with myelodysplasia-related changes

Therapy-related myeloid neoplasms

Acute myeloid leukemia, not otherwise specified

- AML with minimal differentiation
- AML without maturation
- AML with maturation
- Acute myelomonocytic leukemia
- Acute monoblastic/monocytic leukemia
- Acute erythroid leukemias
 - Pure erythroid leukemia
 - Erythroleukemia, erythroid/myeloid
- Acute megakaryoblastic leukemia
- Acute basophilic leukemia
- Acute panmyelosis with myelofibrosis



WHO Classification of ALL

B lymphoblastic leukemia/lymphoma, NOS

B lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities

B lymphoblastic leukemia/lymphoma with t(9;22)(q34;q11.2); *BCR-ABL1*

B lymphoblastic leukemia/lymphoma with t(v;11q23); *MLL* rearranged

B lymphoblastic leukemia/lymphoma with t(12;21)(p13;q22); *TEL-AML1 (ETV6-RUNX1)*

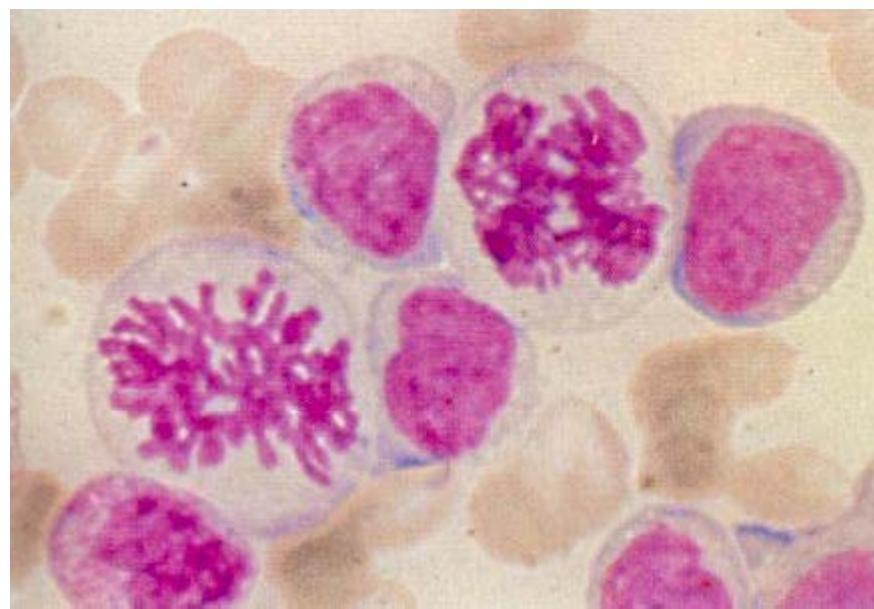
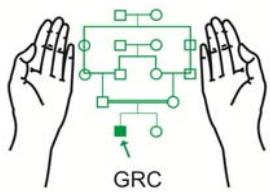
B lymphoblastic leukemia/lymphoma with hyperdiploidy

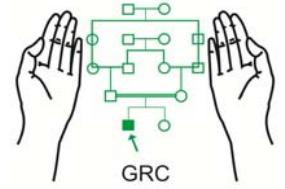
B lymphoblastic leukemia/lymphoma with hypodiploidy (Hypodiploid ALL)

B lymphoblastic leukemia/lymphoma with t(5;14)(q31;q32); *IL3-IGH*

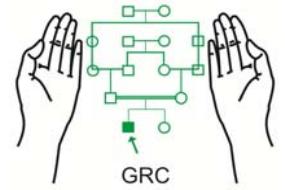
B lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3); *E2A-PBX1 (TCF3-PBX1)*

T lymphoblastic leukemia/lymphoma



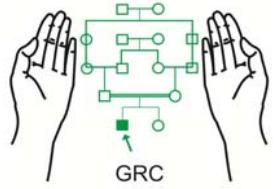


Cancer is almost certainly a genetic disorder



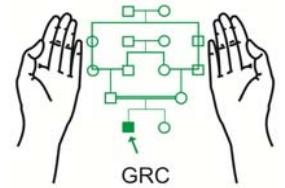
Carcinogenesis

- Oncogenes
 - Chromosomal Translocation
 - Point Mutation
 - Gene Amplification
 - Retroviral Activation
- Tumour Suppressor Genes
- Micro RNA Genes

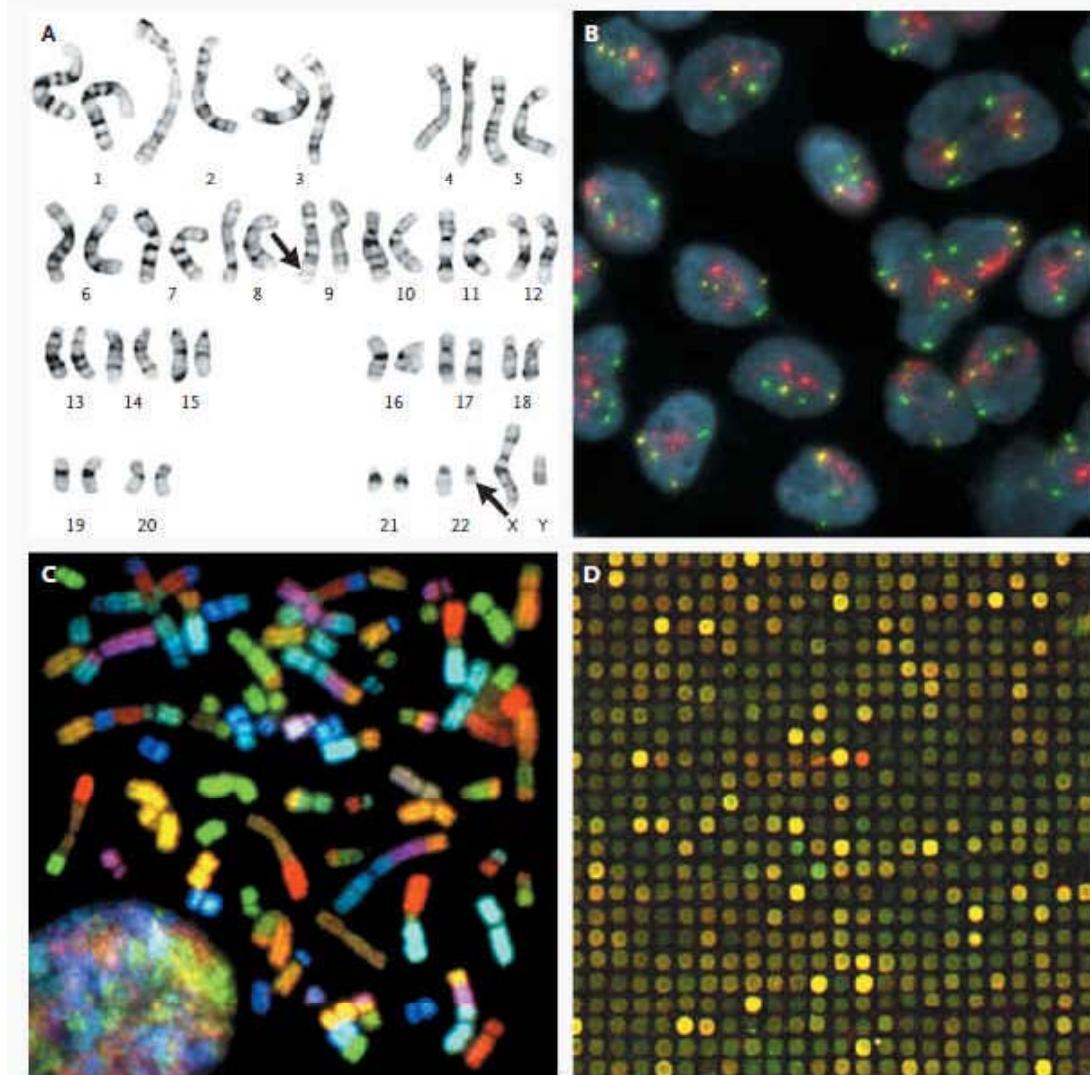


Why Molecular?

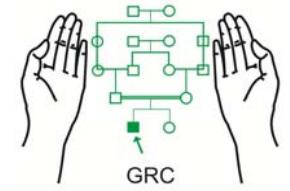
- Diagnosis
- Prognostic Stratification
- Minimal Residual Disease
- Therapy



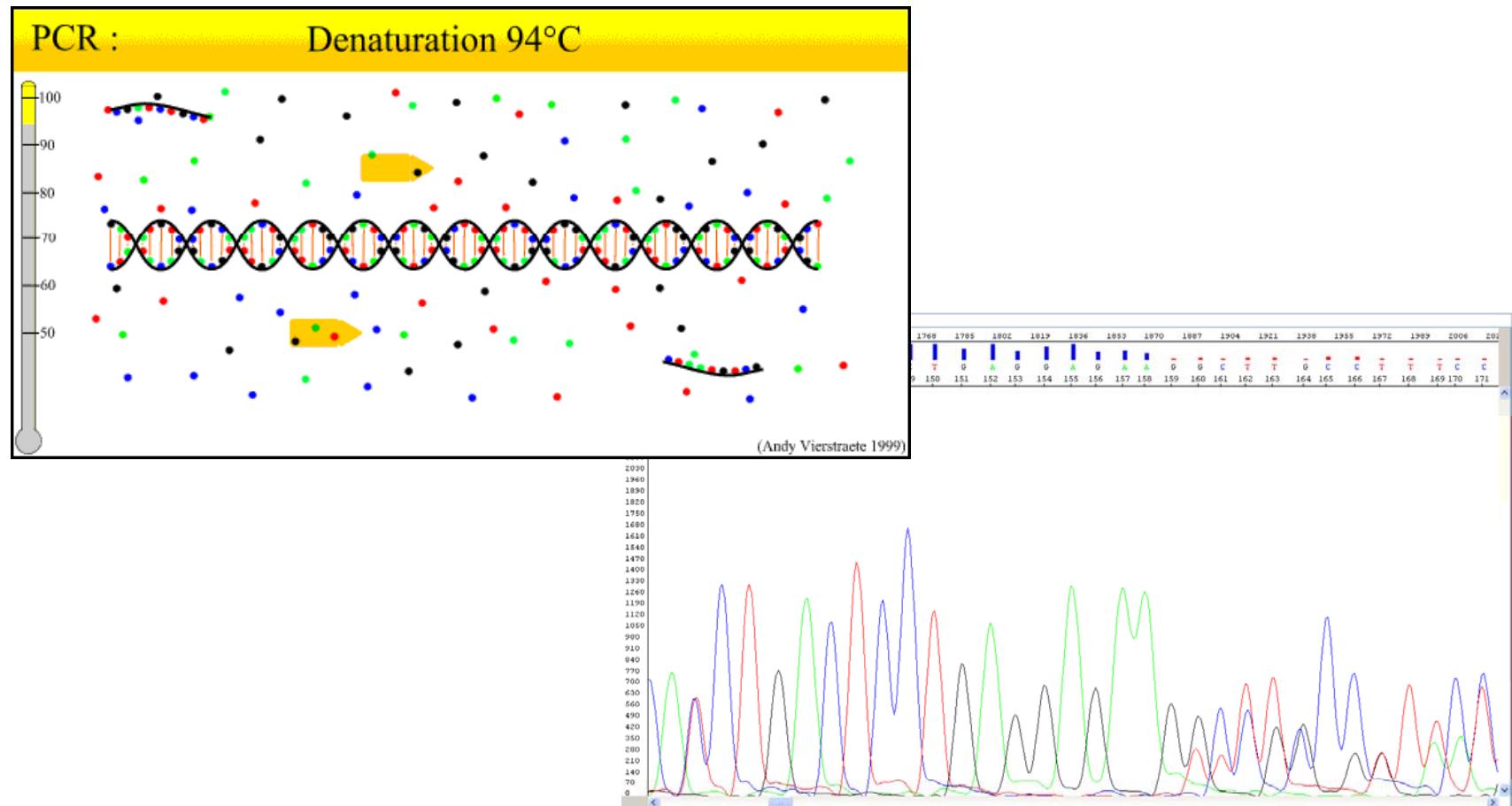
Cytogenetics

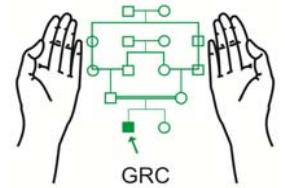


Thomas Ried (2004) Cytogenetics: In Color and Digitized. N Engl J Med 350: 16

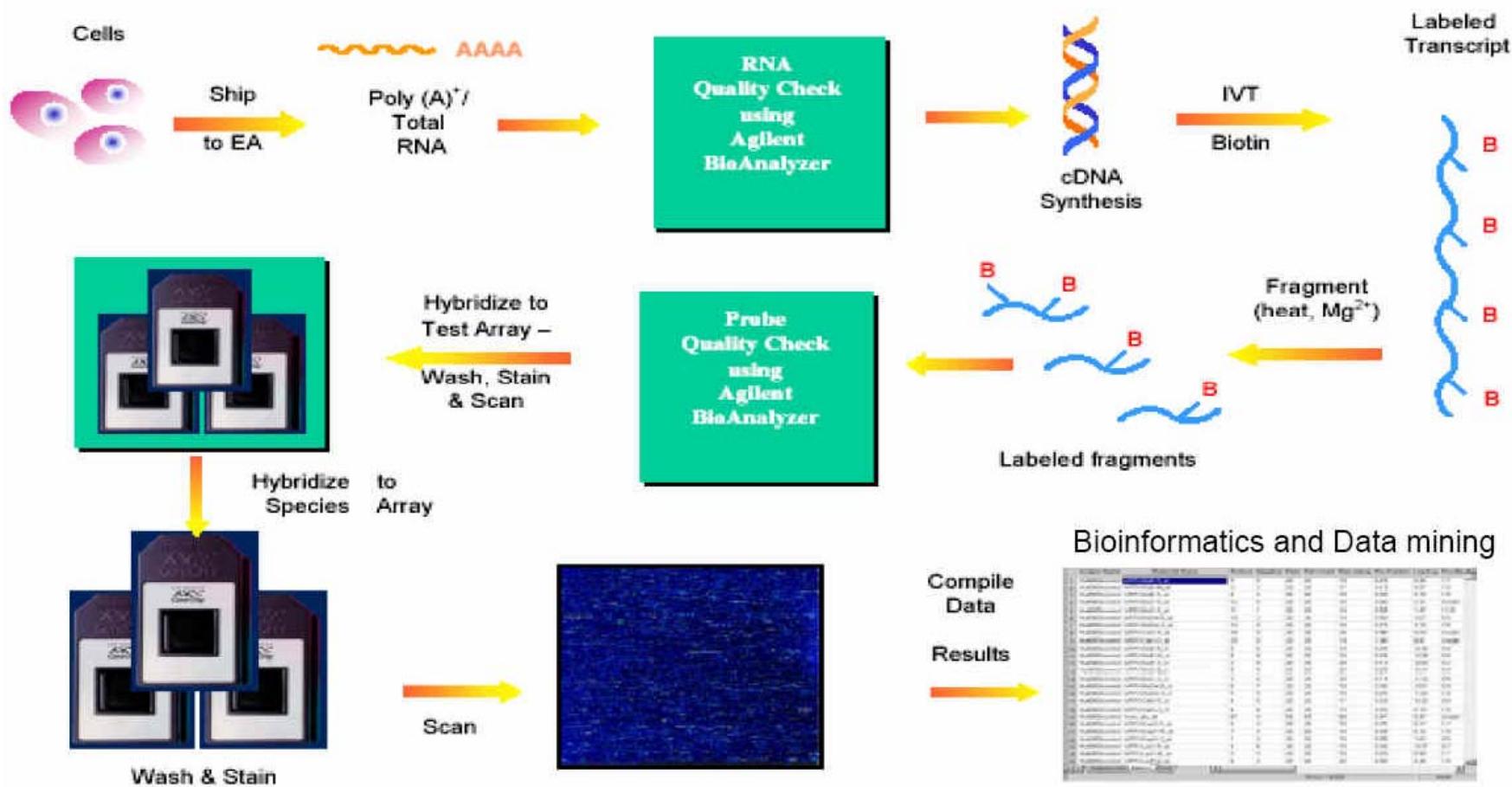


Molecular Genetics

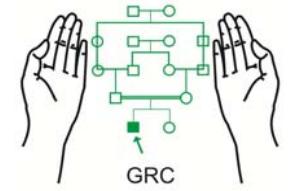




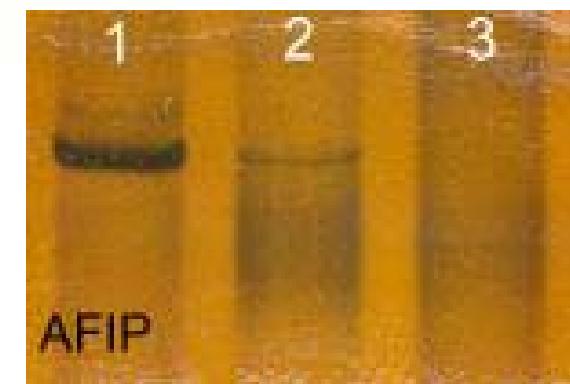
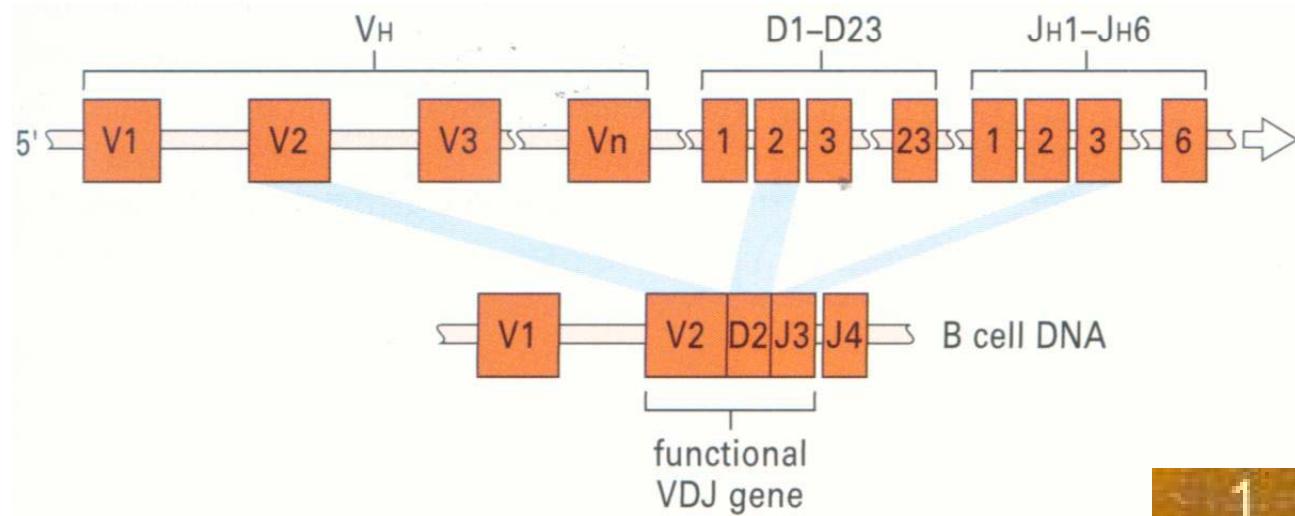
Gene Chips

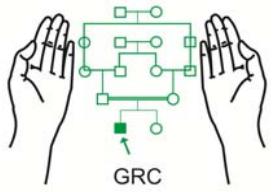


Thomas Ried (2004) Cytogenetics: In Color and Digitized. N Engl J Med 350: 16

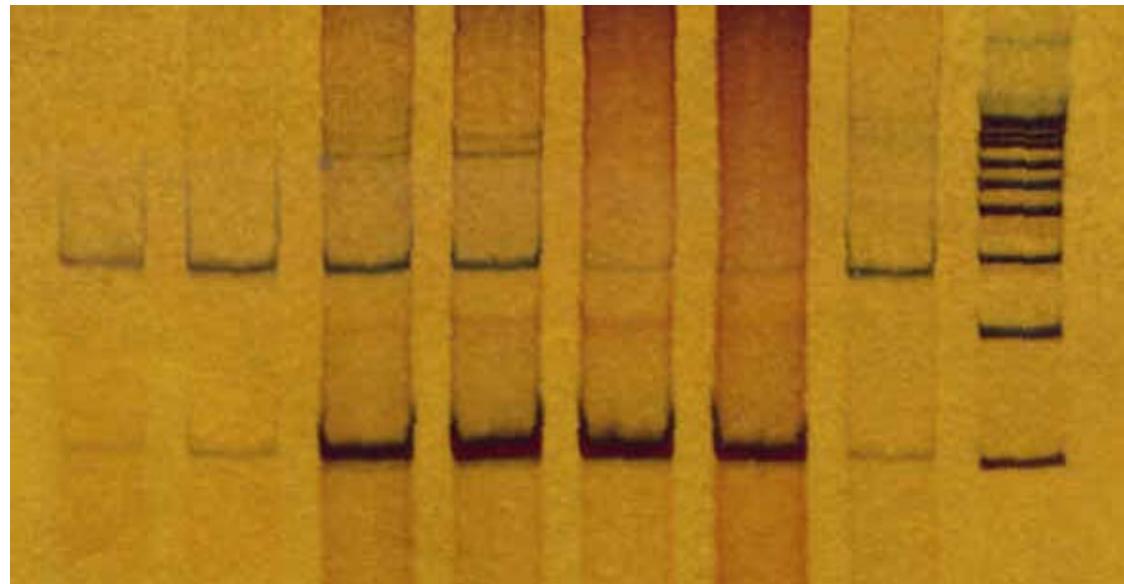


Ig Gene Rearrangements

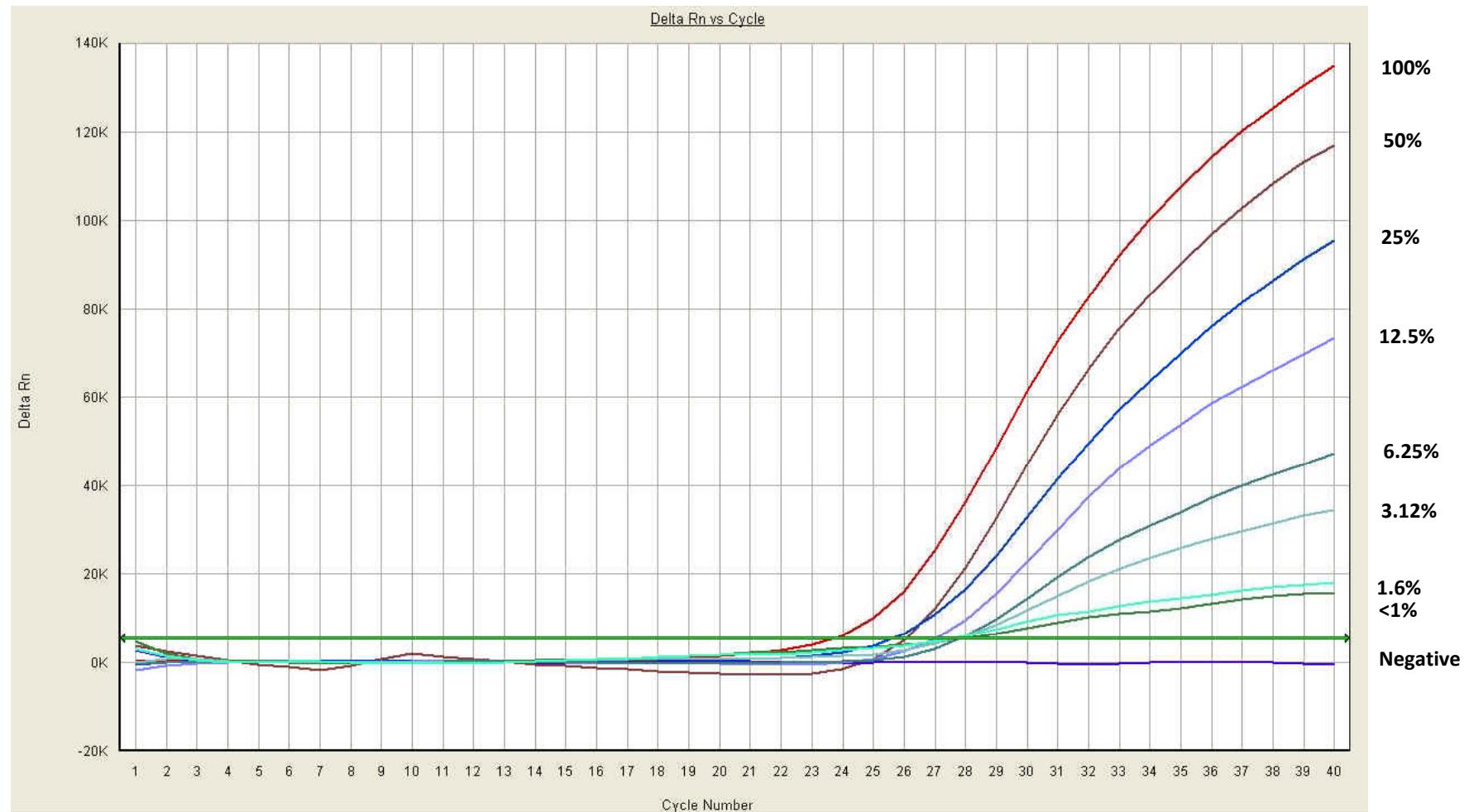
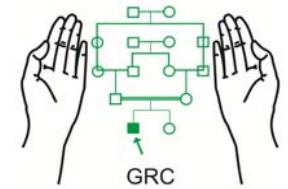


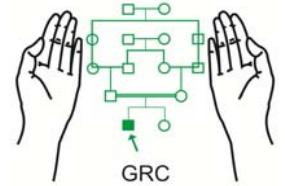


JAK2 Mutation



Real Time PCR for Bcr-abl





PCR for Leukaemia

Chromosome aberration

t(1;19)(q23;p13)
t(4;11)(q21;q23)
t(12;21)(p13;q22)
t(9;22)(q34;q11)
t(9;22)(q34;q11)
del(1)(p32p32)
t(15;17)(q22;q21)
inv(16)(p13q22)
t(8;21)(q22;q22)

RQ-PCR target

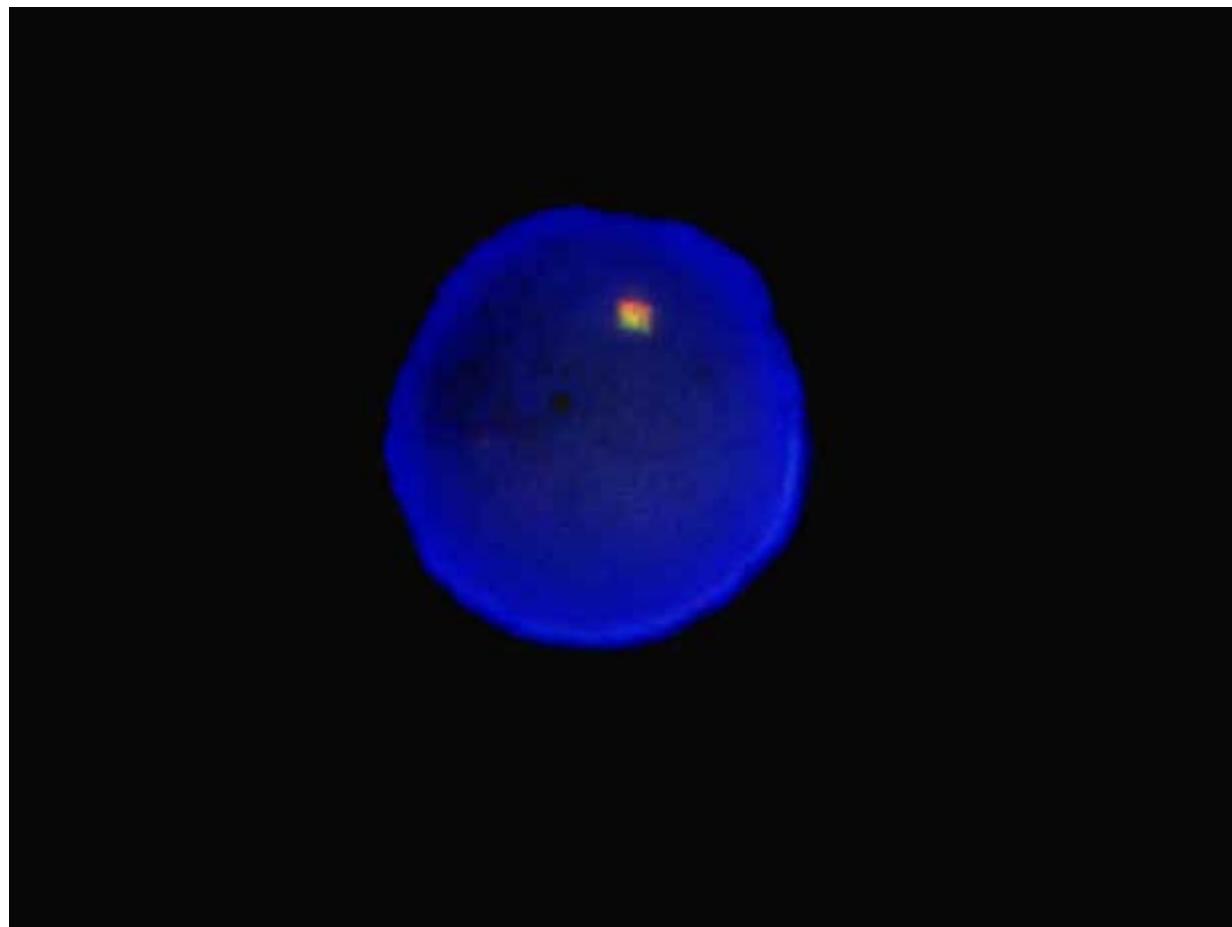
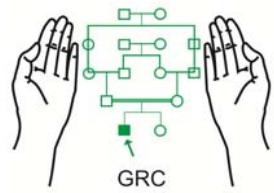
E2A-PBX1
MLL-AF4
TEL-AML1
BCR-ABL m-bcr
BCR-ABL M-bcr
SIL-TAL1
PML-RARA
CBFB-MYH11
AML1-ETO

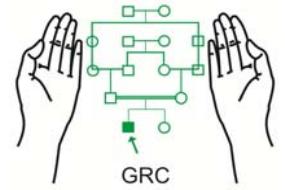
ALL

AML

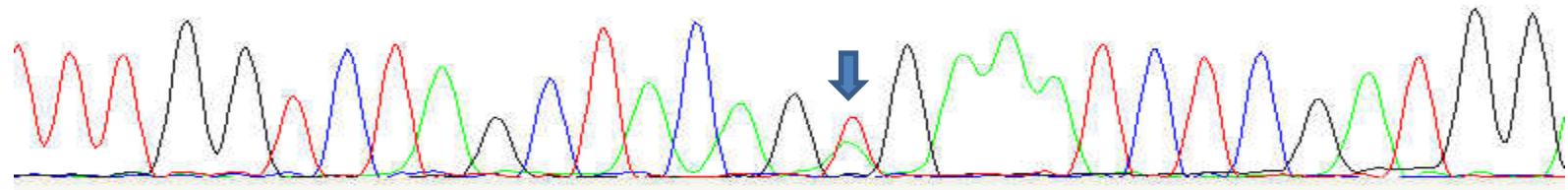
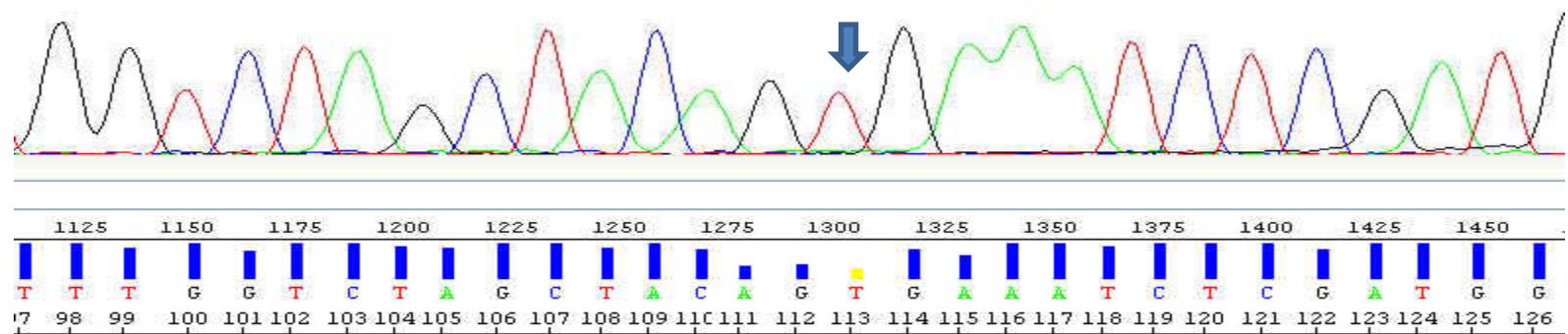
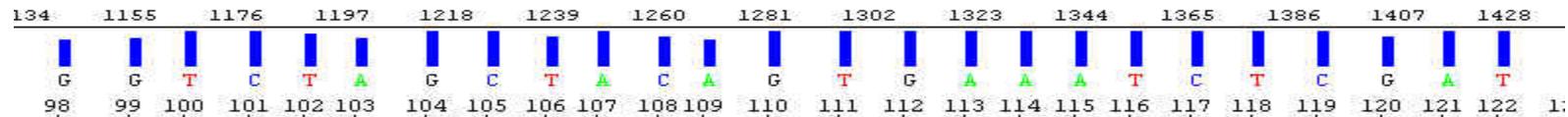
(Gabert et al, (2003) Leukaemia 17: 2318-2357)

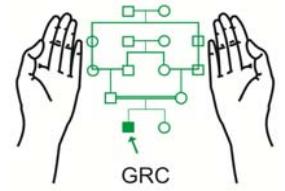
FISH



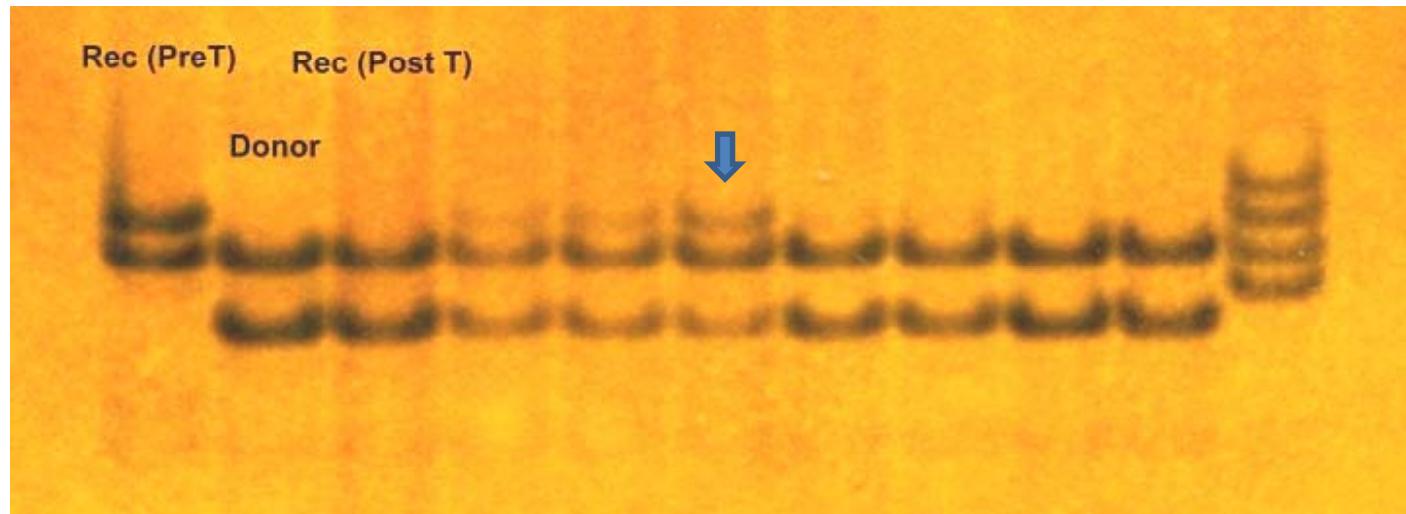


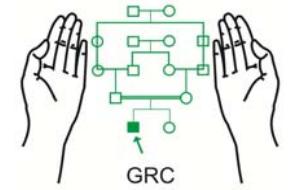
BRAF Mutation





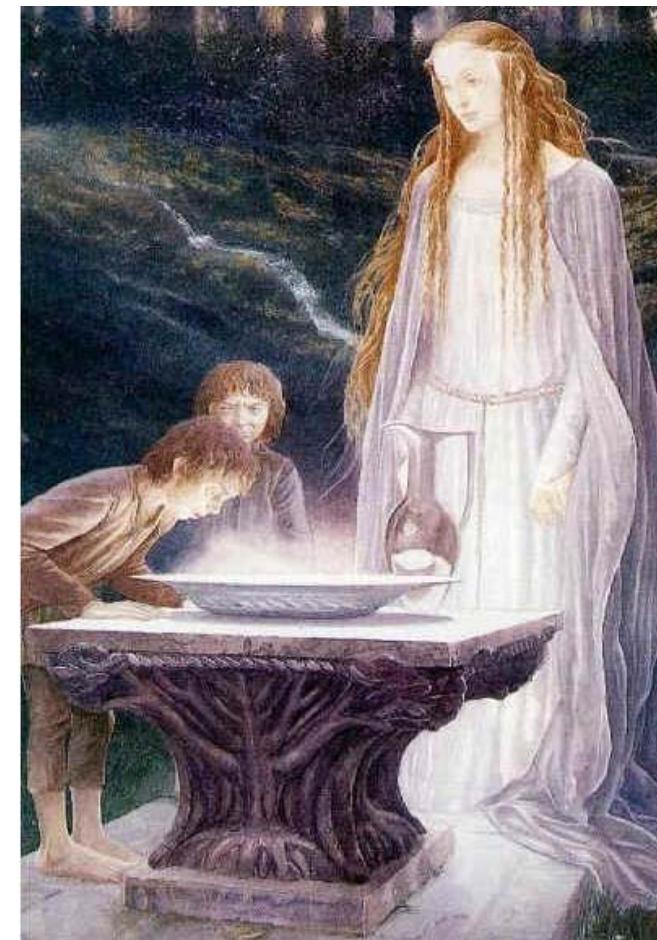
Donor Chimerism

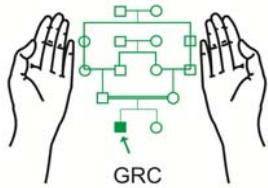




The Mirror of Galadriel

The Mirror of Galadriel was a silver basin of water which could show the viewer events in the past, present or even the future.





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EDITORIAL

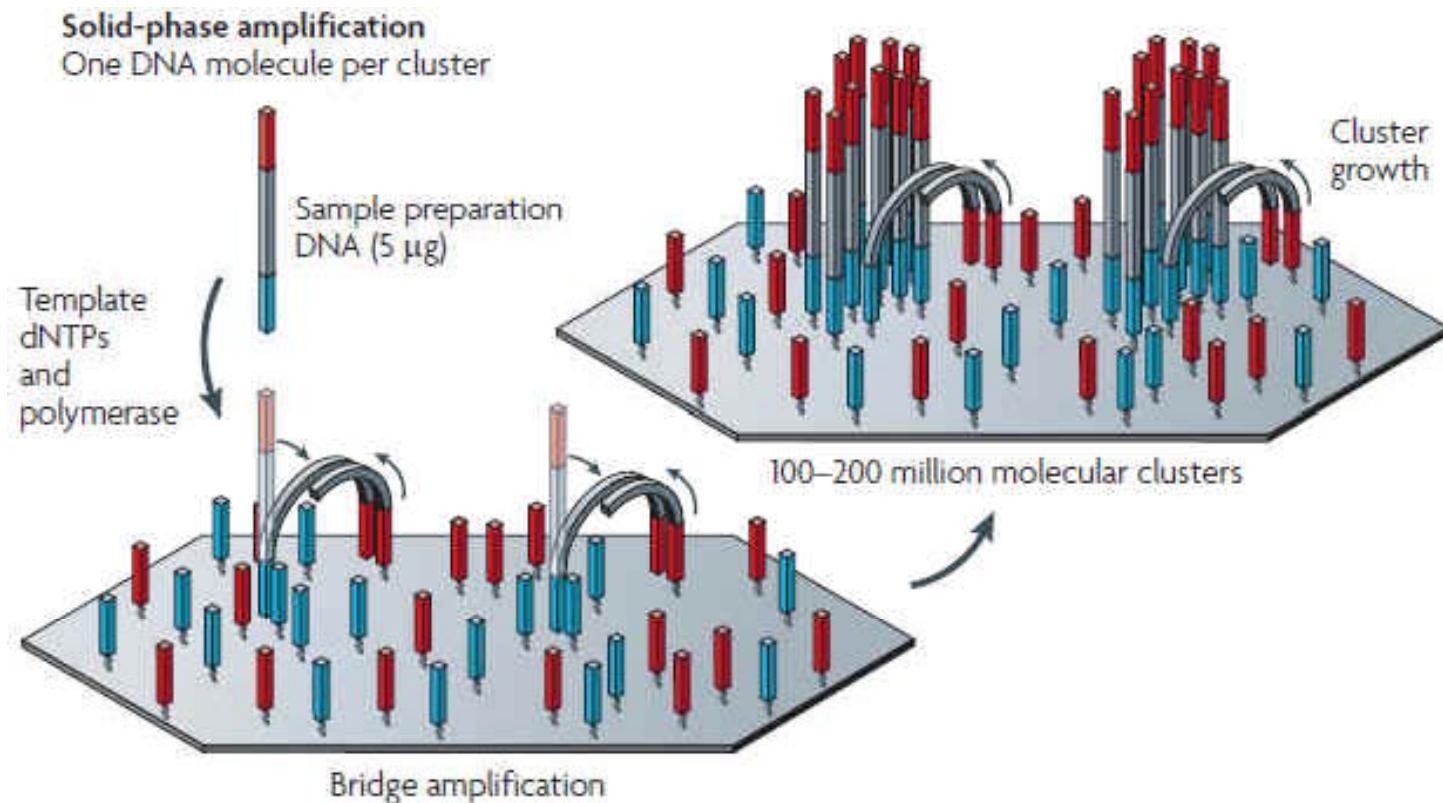


Individual Genomes on the Horizon

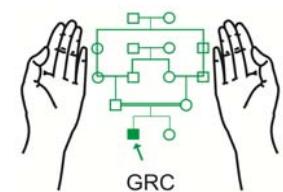
Richard P. Lifton, M.D., Ph.D.

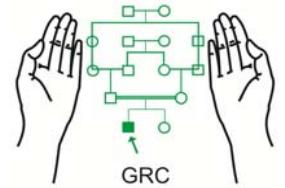
N Engl J Med 2010; 362: 1235-1236

Next Generation Sequencing (NGS)

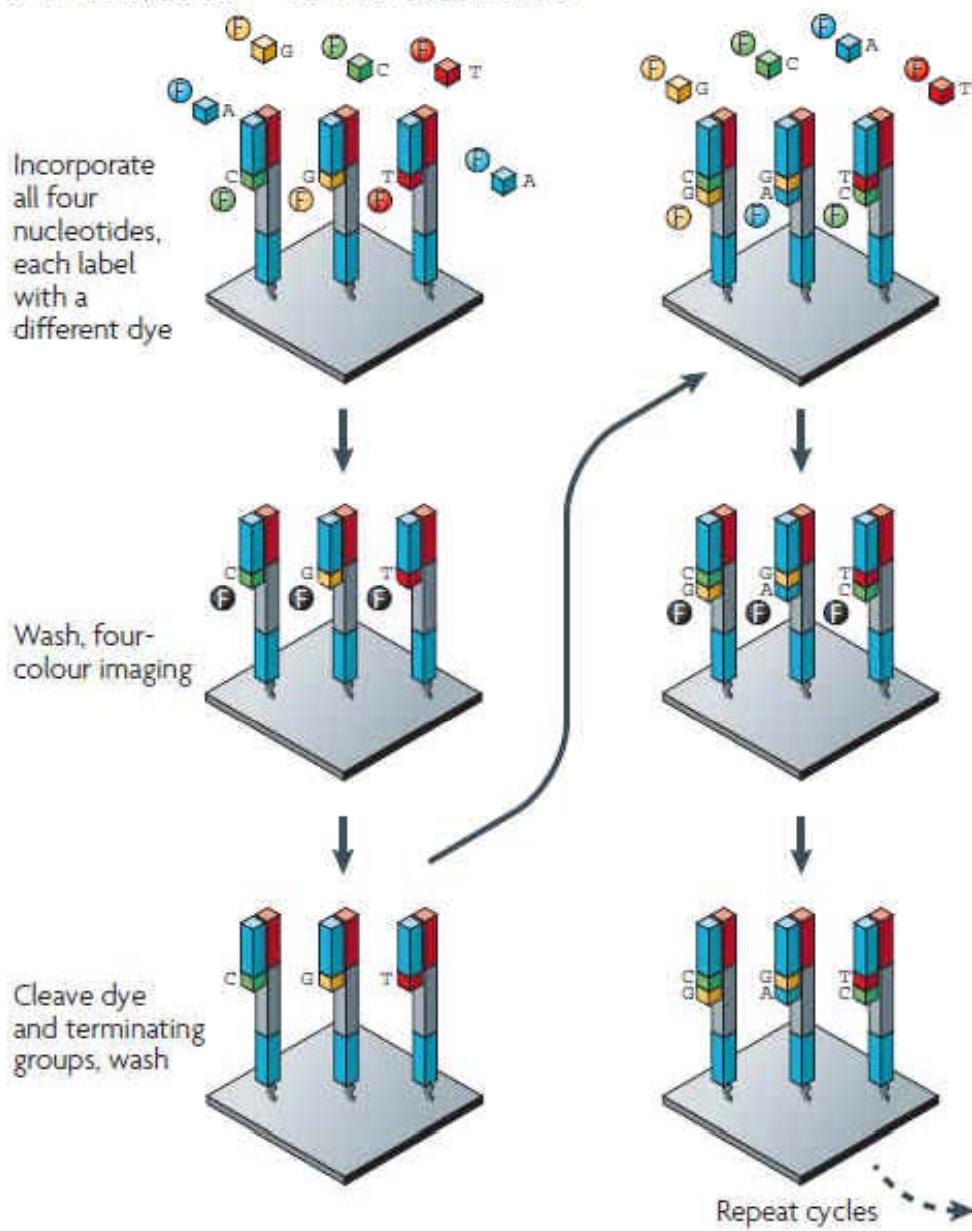


Michael L. Metzker (2010) Nature Reviews Genetics 11: 31-46

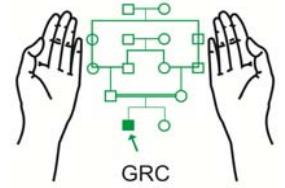




a Illumina/Solexa — Reversible terminators



Michael L. Metzker (2010) Nature Reviews Genetics 11: 31-46



- Application of an ever increasing number of immunologic markers, in order to better classify malignant lymphomas, will eventually result in the reverse, namely, in a complete breakup of this group of malignancies into individual cases.

Metz & Leder (1985) Cancer 56: 1392-95