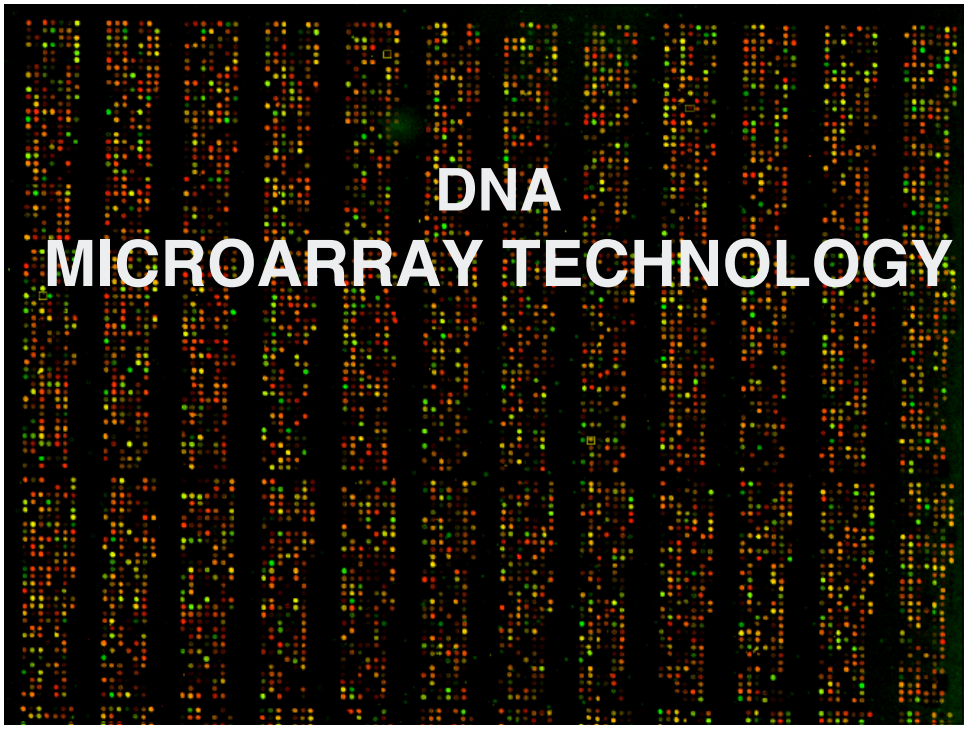


Cancer Genetics Branch

AFTER THE SEQUENCE:
WHOLE GENOME APPROACHES TO BIOLOGICAL QUESTIONS

GENE EXPRESSION

GENE VARIATION

GENE FUNCTION

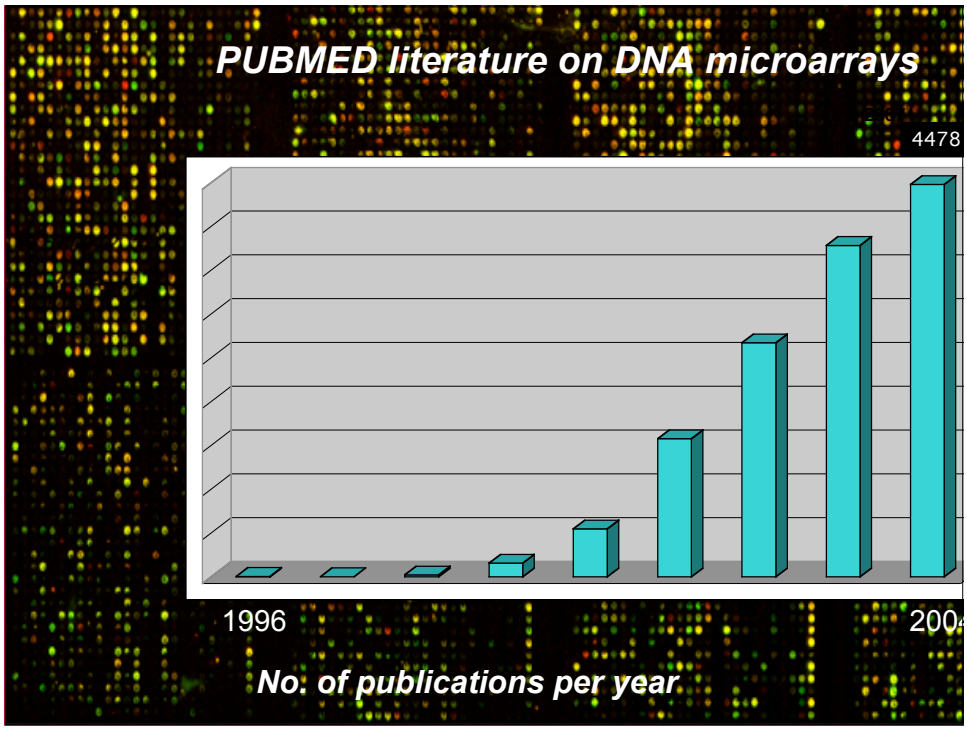
National Human Genome Research Institute

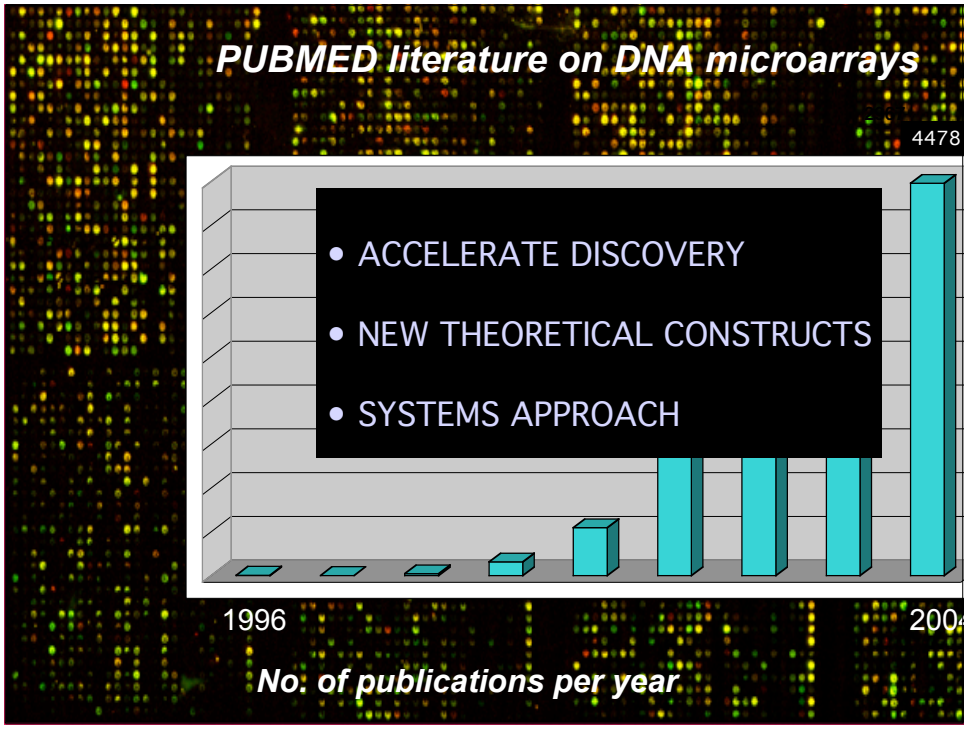
Cancer Genetics Branch

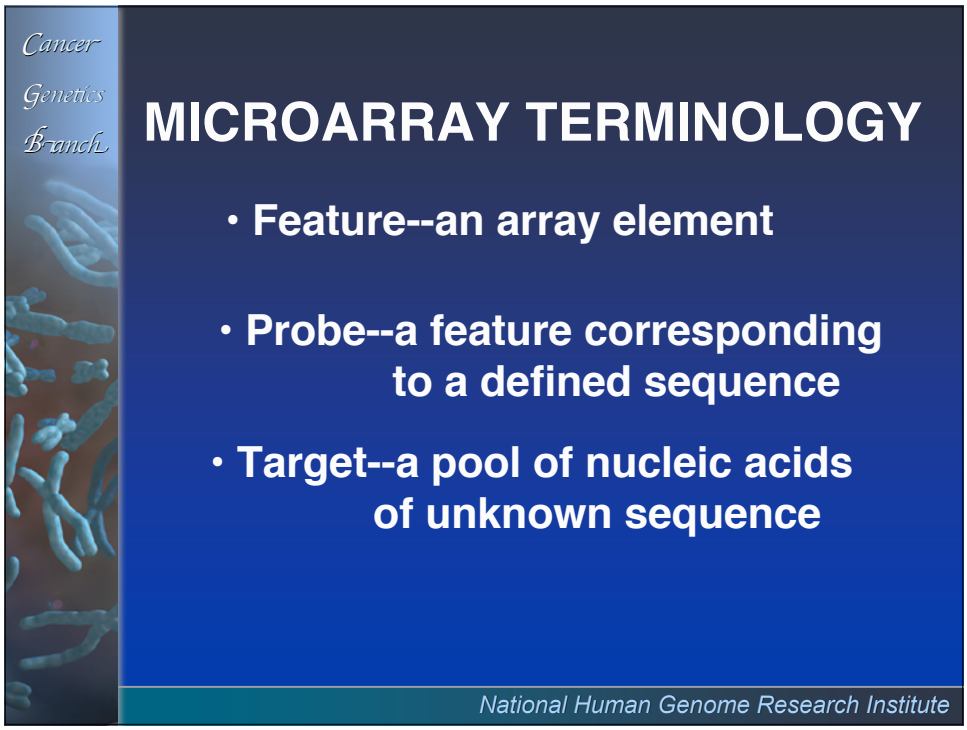
MICROARRAYS PROVIDE A TOOL FOR WHOLE GENOME ANALYSIS

PRIMARY IMPACT: ACCELERATED DISCOVERY AND HYPOTHESIS GENERATION

National Human Genome Research Institute




PUBMED literature on DNA microarrays
4478
• ACCELERATE DISCOVERY
• NEW THEORETICAL CONSTRUCTS
• SYSTEMS APPROACH
1996
No. of publications per year


Cancer Genetics Branch
MICROARRAY TERMINOLOGY
• Feature--an array element
• Probe--a feature corresponding to a defined sequence
• Target--a pool of nucleic acids of unknown sequence
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POSSIBLE ARRAY FEATURES

- Synthetic Oligonucleotides
- PCR products from
  - Cloned DNAs
  - Genomic DNA
- Cloned DNA

National Human Genome Research Institute

Cancer Genetics Branch

Microarray Manufacture

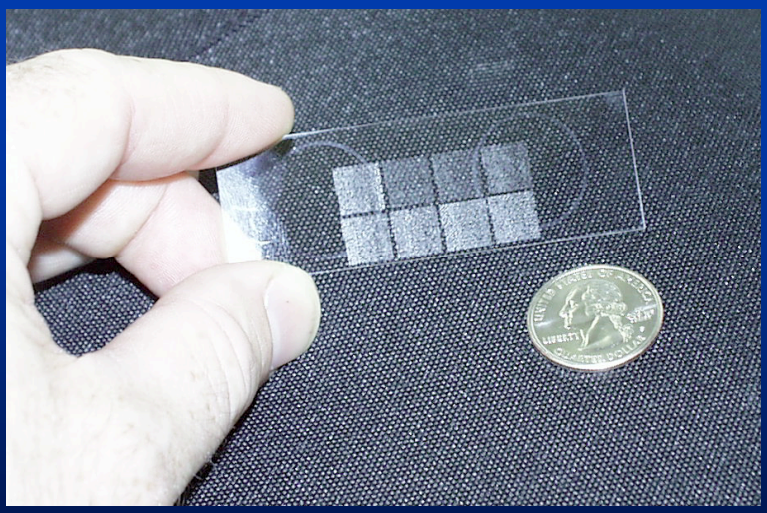
- Printing

National Human Genome Research Institute

Cancer Genetics Branch

National Human Genome Research Institute

Cancer Genetics Branch



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Cancer Genetics Branch

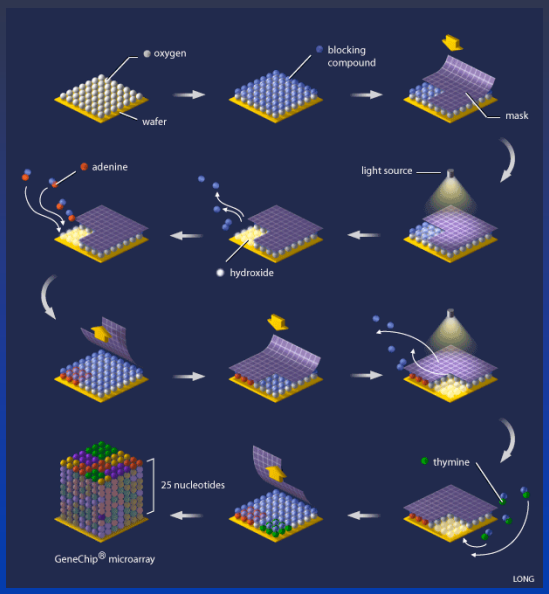
Microarray Manufacture

- Printing
- Synthesis *in situ*

National Human Genome Research Institute

Cancer Genetics Branch

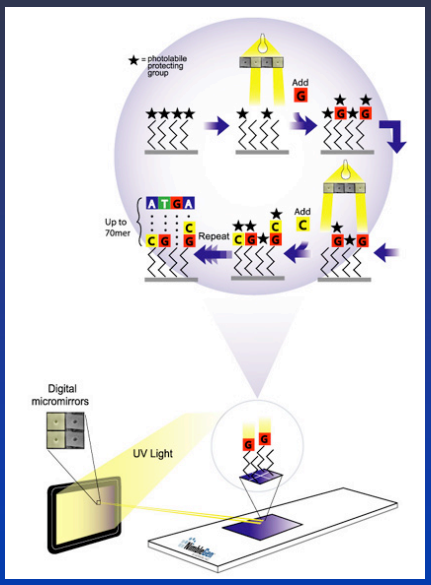
LIGHT DIRECTED OLIGONUCLEOTIDE SYNTHESIS



National Human Genome Research Institute

Cancer Genetics Branch

LIGHT DIRECTED OLIGONUCLEOTIDE SYNTHESIS



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MICROARRAY READOUT

- Determine quantity of target bound to each probe in a complex hybridization
- Must have high sensitivity, low background
- High spatial resolution essential
- Dual channel capability
- Fluorescent tags meet these demands

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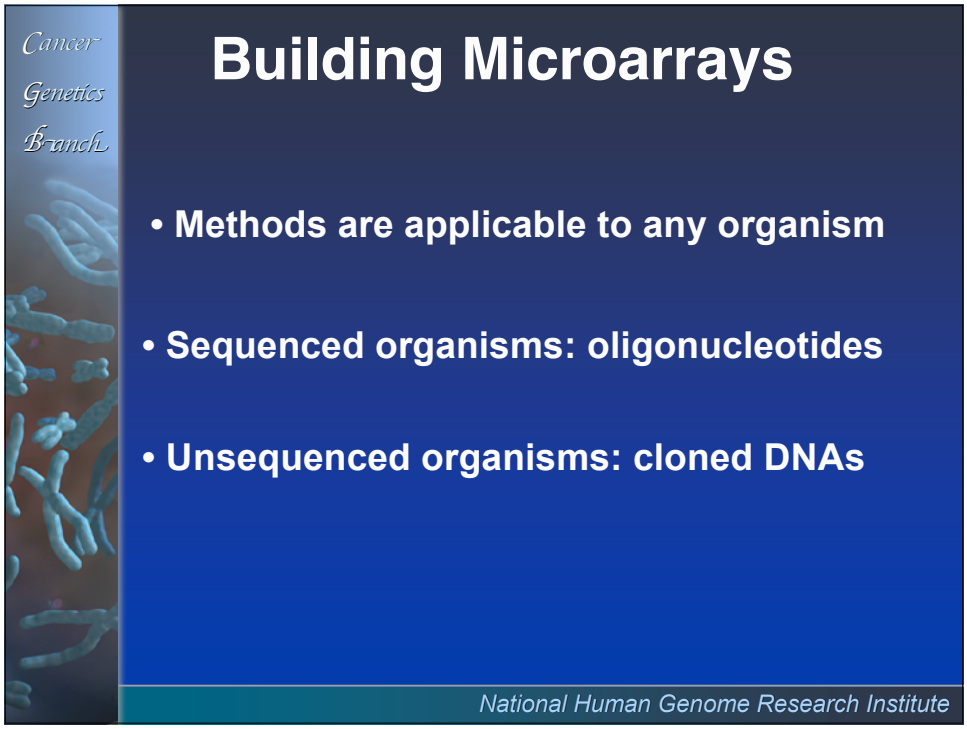
Cancer Genetics Branch
Building Microarrays
• Methods are applicable to any organism
• Sequenced organisms: oligonucleotides
• Unsequenced organisms: cloned DNAs
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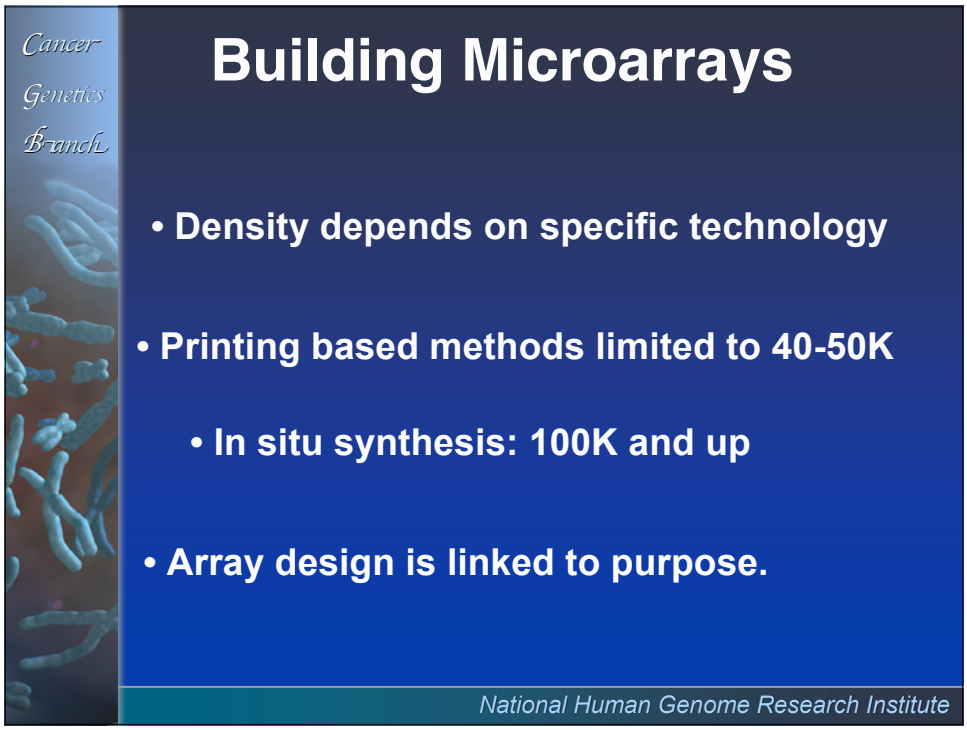
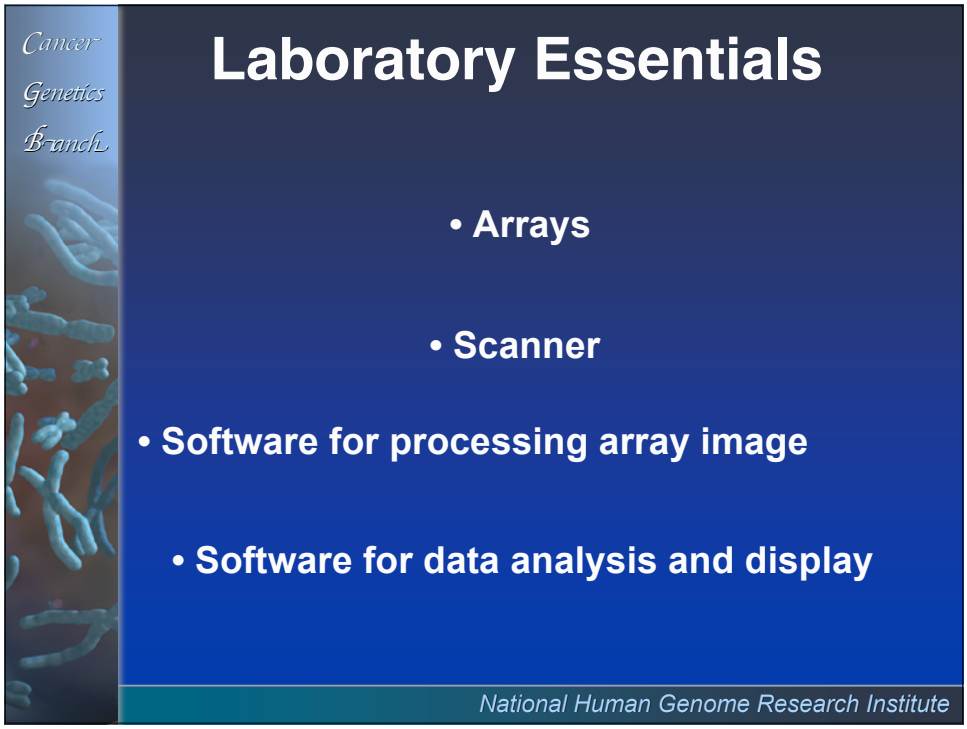

Cancer Genetics Branch
Building Microarrays
• Density depends on specific technology
• Printing based methods limited to 40-50K
• In situ synthesis: 100K and up
• Array design is linked to purpose.
National Human Genome Research Institute


Cancer Genetics Branch
Laboratory Essentials
• Arrays
• Scanner
• Software for processing array image
• Software for data analysis and display
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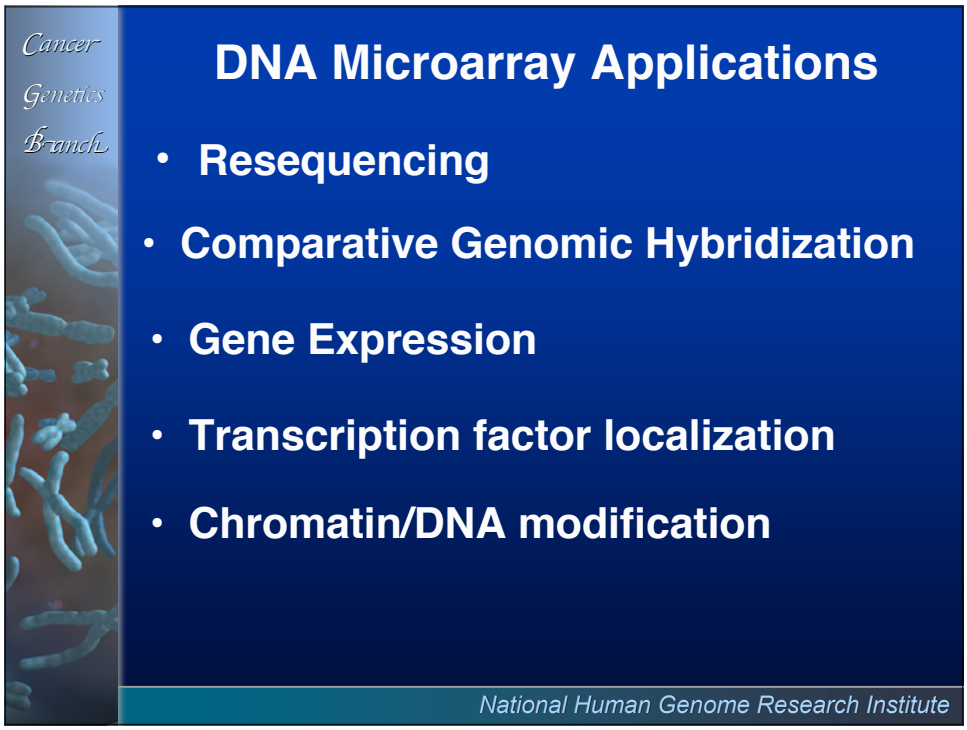
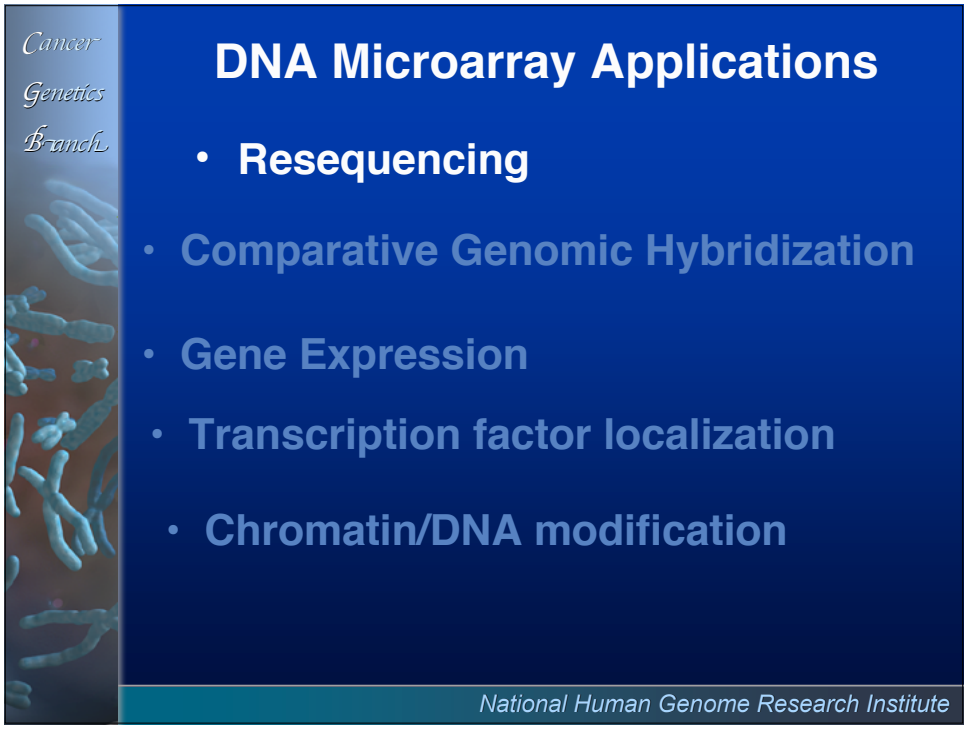
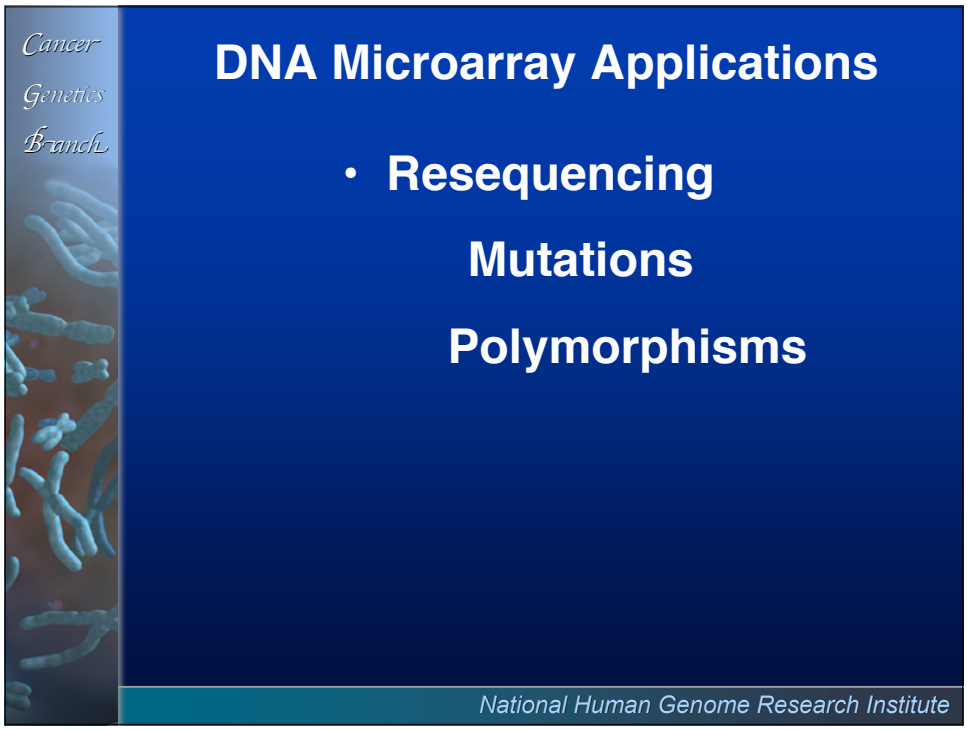
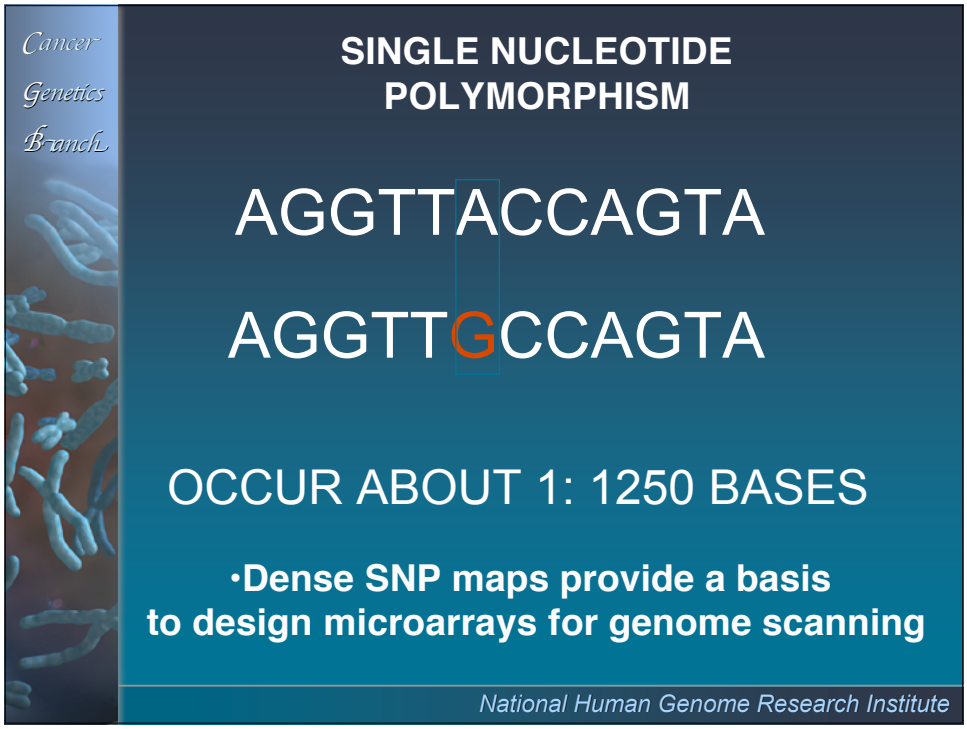
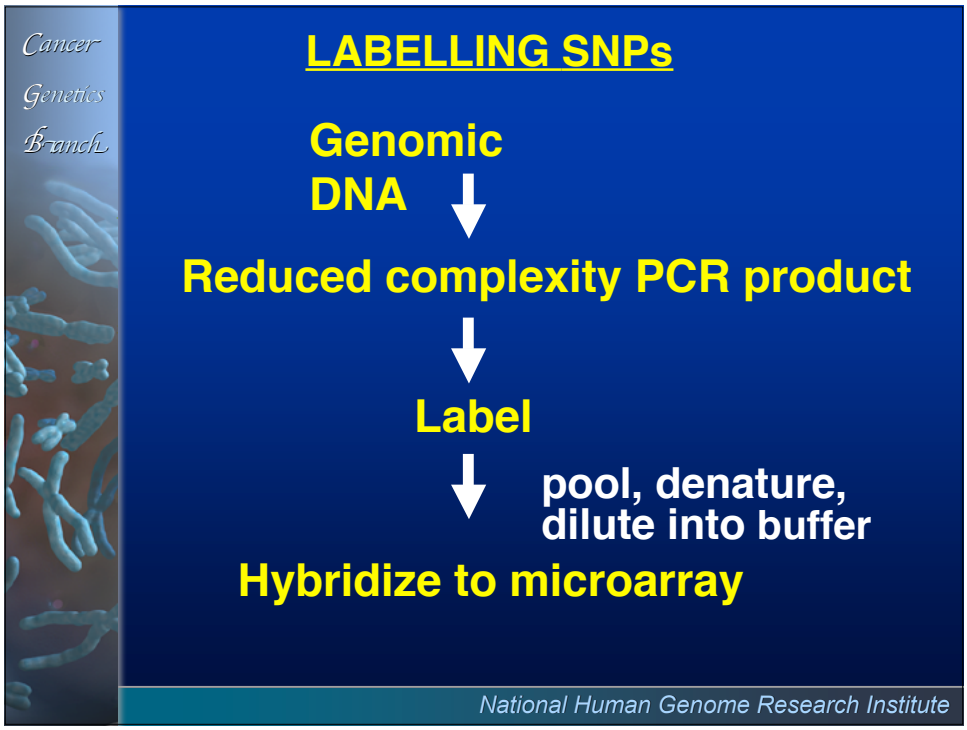

Cancer Genetics Branch
DNA Microarray Applications
• Resequencing
• Comparative Genomic Hybridization
• Gene Expression
• Transcription factor localization
• Chromatin/DNA modification
National Human Genome Research Institute


Cancer Genetics Branch
DNA Microarray Applications
• Resequencing
• Comparative Genomic Hybridization
• Gene Expression
• Transcription factor localization
• Chromatin/DNA modification
National Human Genome Research Institute

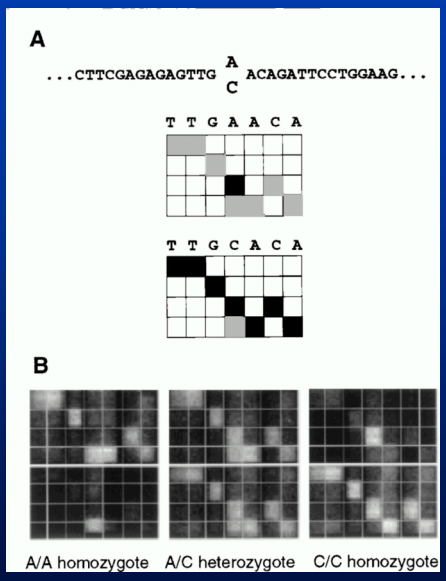

Cancer Genetics Branch
DNA Microarray Applications
• Resequencing
Mutations
Polymorphisms
National Human Genome Research Institute


Cancer Genetics Branch
SINGLE NUCLEOTIDE POLYMORPHISM
AGGTTACCAGTA
AGGTTGCCAGTA
OCCUR ABOUT 1: 1250 BASES
•Dense SNP maps provide a basis to design microarrays for genome scanning
National Human Genome Research Institute


Cancer Genetics Branch
LABELLING SNPs
Genomic DNA
Reduced complexity PCR product
Label
pool, denature, dilute into buffer
Hybridize to microarray
National Human Genome Research Institute

Cancer Genetics Branch

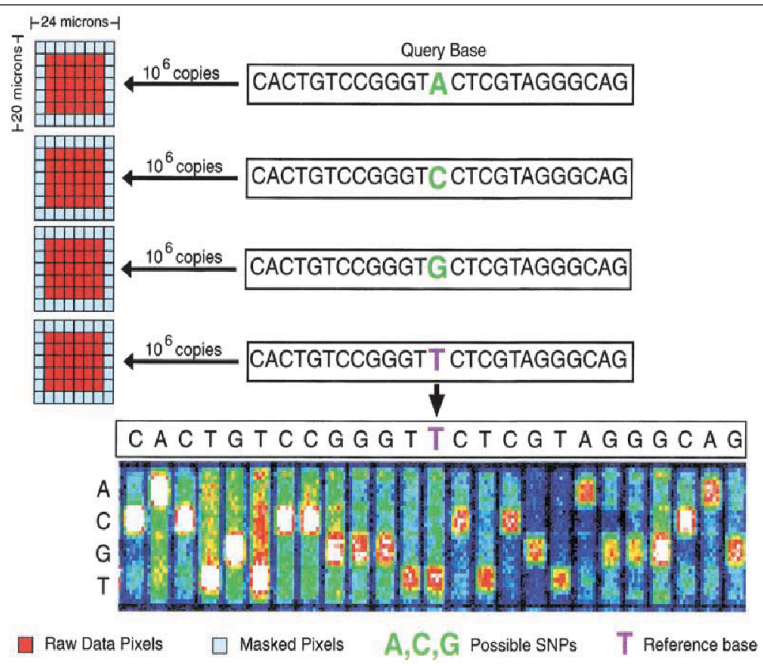
SNP CHIP*



*Wang et al.
Science 280:1077
1998

National Human Genome Research Institute

Cancer Genetics Branch



Cutler DJ et al. Genome Res. 2001 11:1913-25.

National Human Genome Research Institute

Cancer Genetics Branch

ACCURACY OF SNP CHIP

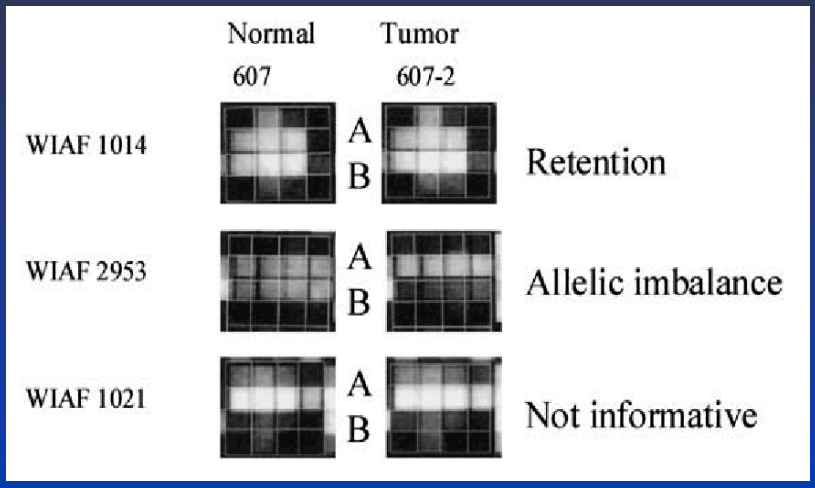
Table 3. ABACUS SNP Detection and Genotyping Accuracy

	Verified	Total Possible
A. Accuracy of autosomal SNPs detection		
Singleton SNPs	17	17
Non-singleton SNPs	91	91
Total SNPs	108	108
B. Number of autosomal SNPs electronically verified		
Number of SNPs electronically verified	371	
C. Accuracy of autosomal genotype calls		
Number of verified homozygous genotype calls	1515	
Number of incorrect homozygous genotype calls	0	
Percent correct homozygote calls	100.00%	
Number of verified heterozygous genotype calls	423	
Number of incorrect heterozygous genotype calls	3	
Percent correct heterozygote calls	99.30%	
D. Accuracy of haploid genotype calls		
Number of bases sequenced (6X coverage)	17,423	
Number of bases different from microarray chip calls	0	
Percent of bases identical	100.00%	

Cutler DJ et al. Genome Res. 2001 11:1913-25.

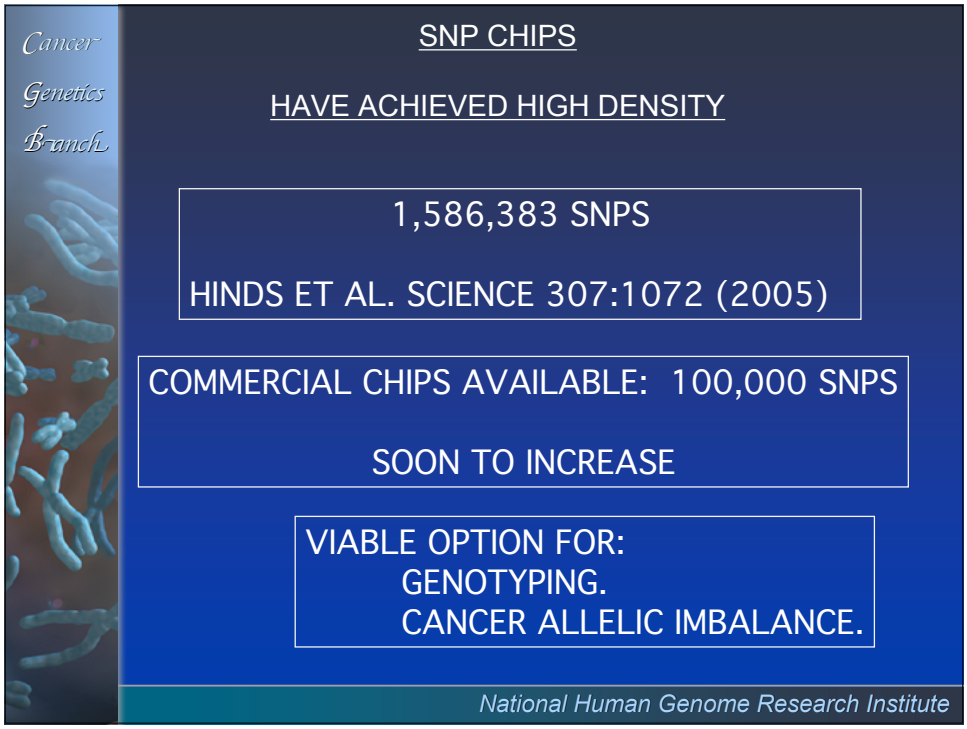
Cancer Genetics Branch

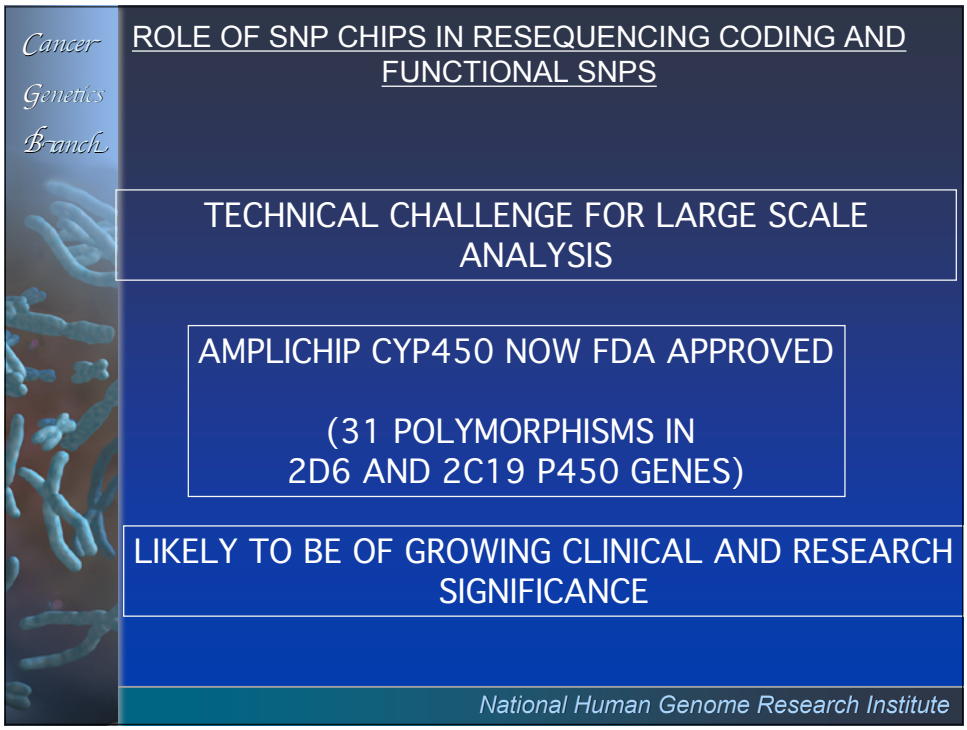
SNP CHIP FOR ALLELIC IMBALANCE

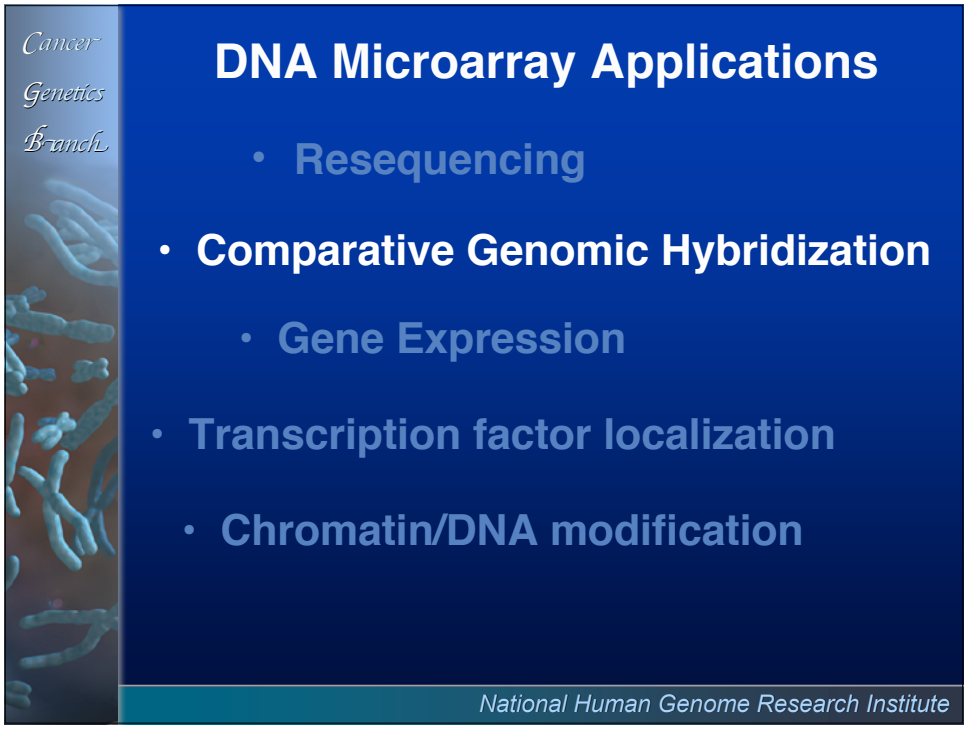


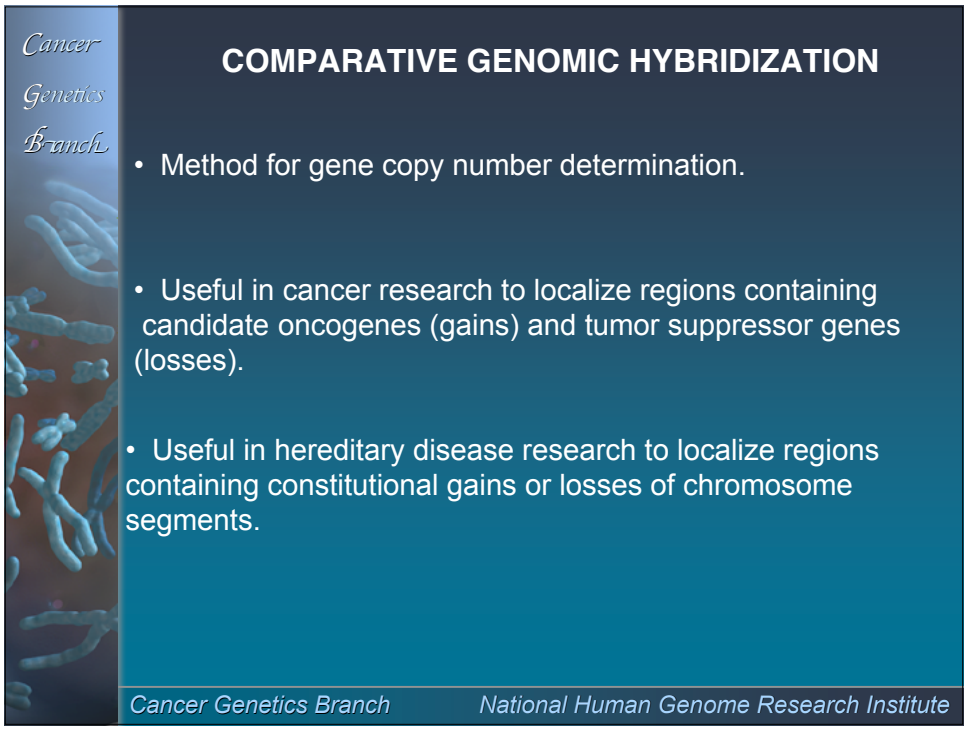
Primdahl Het al. J Natl Cancer Inst. 2002, 94:216-223

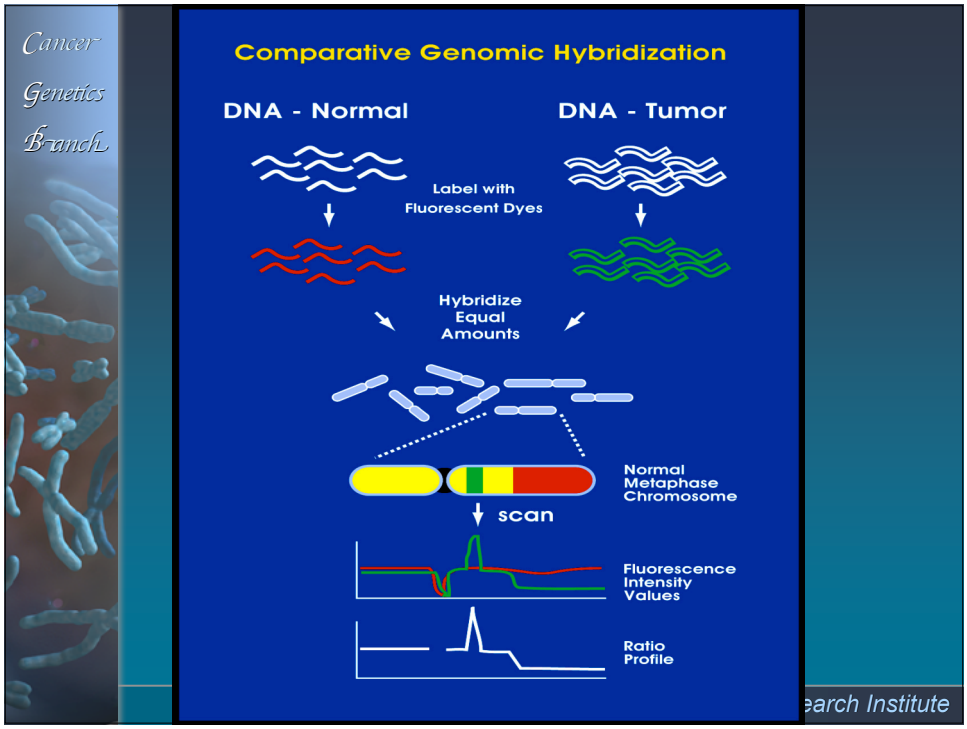
National Human Genome Research Institute

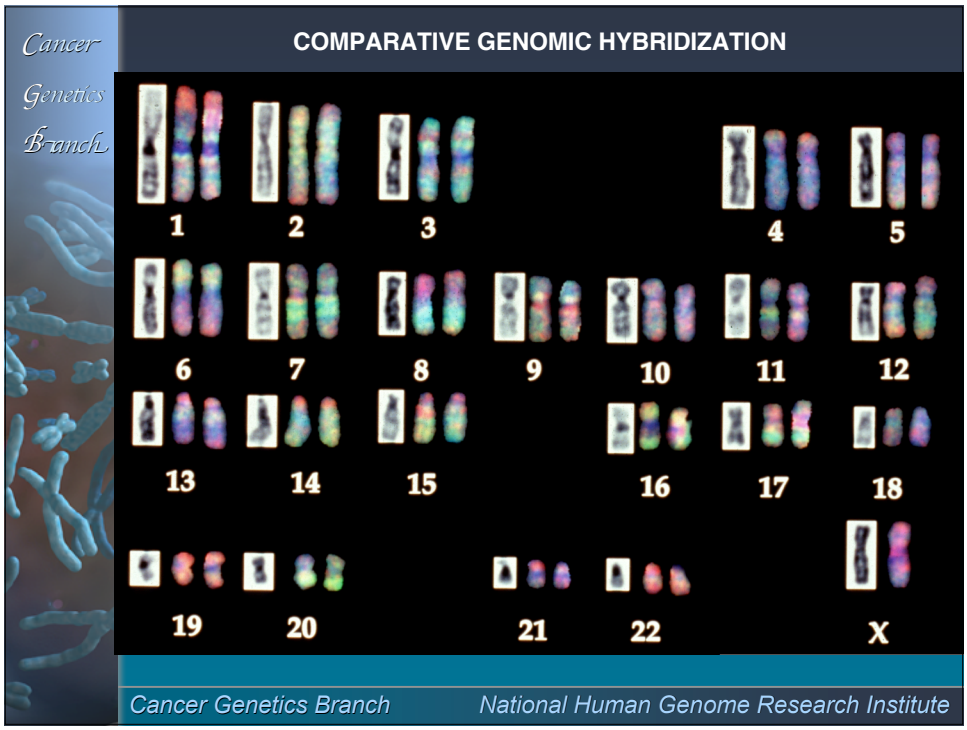

Cancer Genetics Branch
SNP CHIPS
HAVE ACHIEVED HIGH DENSITY
1,586,383 SNPS
HINDS ET AL. SCIENCE 307:1072 (2005)
COMMERCIAL CHIPS AVAILABLE: 100,000 SNPS
SOON TO INCREASE
VIABLE OPTION FOR:
GENOTYPING.
CANCER ALLELIC IMBALANCE.
National Human Genome Research Institute

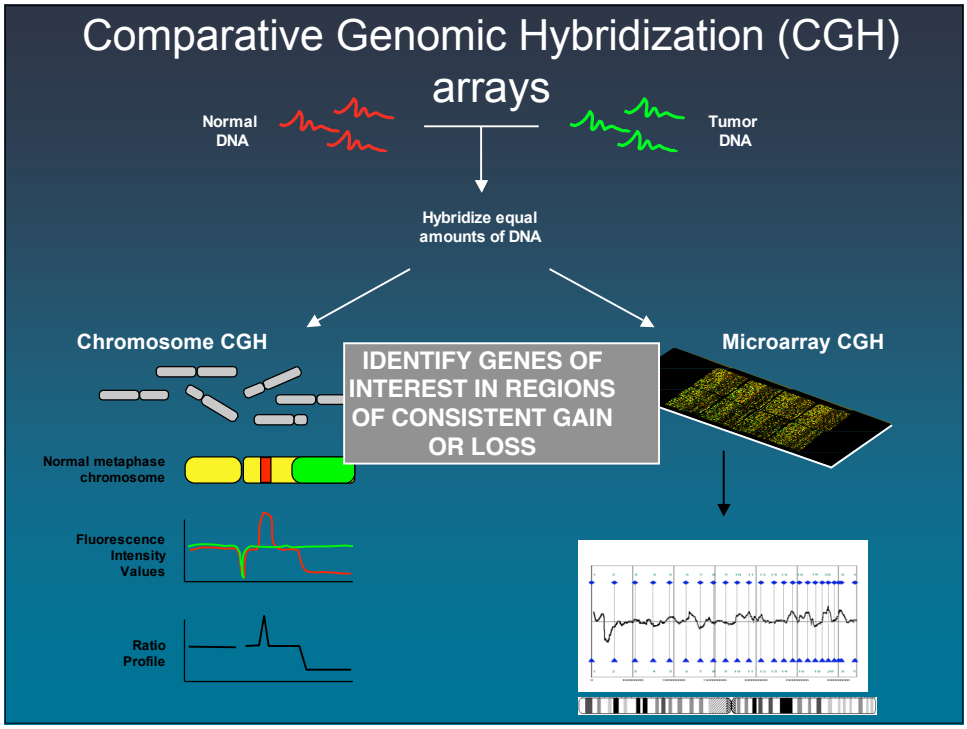

Cancer Genetics Branch
ROLE OF SNP CHIPS IN RESEQUENCING CODING AND FUNCTIONAL SNPS
TECHNICAL CHALLENGE FOR LARGE SCALE ANALYSIS
AMPLICHIP CYP450 NOW FDA APPROVED
(31 POLYMORPHISMS IN 2D6 AND 2C19 P450 GENES)
LIKELY TO BE OF GROWING CLINICAL AND RESEARCH SIGNIFICANCE
National Human Genome Research Institute

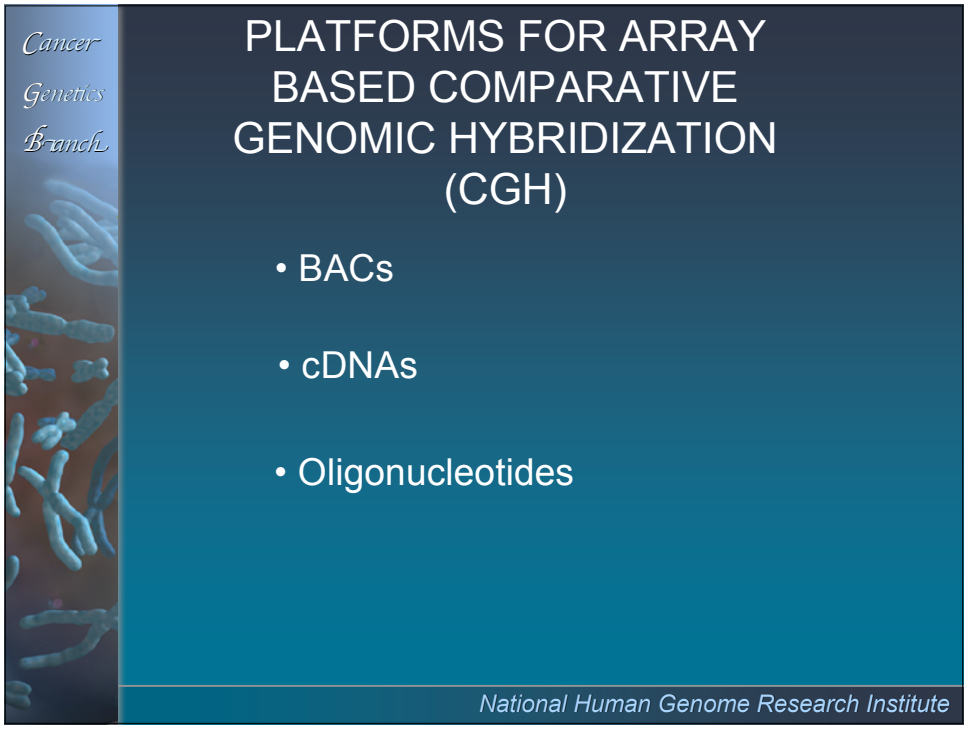

Cancer Genetics Branch
DNA Microarray Applications
• Resequencing
• Comparative Genomic Hybridization
• Gene Expression
• Transcription factor localization
• Chromatin/DNA modification
National Human Genome Research Institute


Cancer Genetics Branch
COMPARATIVE GENOMIC HYBRIDIZATION
• Method for gene copy number determination.
• Useful in cancer research to localize regions containing candidate oncogenes (gains) and tumor suppressor genes (losses).
• Useful in hereditary disease research to localize regions containing constitutional gains or losses of chromosome segments.
Cancer Genetics Branch
National Human Genome Research Institute


Cancer Genetics Branch
Comparative Genomic Hybridization
DNA - Normal
DNA - Tumor
Label with Fluorescent Dyes
Hybridize Equal Amounts
Normal Metaphase Chromosome
scan
Fluorescence Intensity Values
Ratio Profile
earch Institute


Cancer Genetics Branch
COMPARATIVE GENOMIC HYBRIDIZATION
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
X
Cancer Genetics Branch
National Human Genome Research Institute


Comparative Genomic Hybridization (CGH) arrays
Normal DNA
Tumor DNA
Hybridize equal amounts of DNA
Chromosome CGH
Microarray CGH
IDENTIFY GENES OF INTEREST IN REGIONS OF CONSISTENT GAIN OR LOSS
Normal metaphase chromosome
Fluorescence Intensity Values
Ratio Profile


Cancer Genetics Branch
PLATFORMS FOR ARRAY BASED COMPARATIVE GENOMIC HYBRIDIZATION (CGH)
• BACs
• cDNAs
• Oligonucleotides
National Human Genome Research Institute

Cancer Genetics Branch

ARRAY CGH

- HIGH RESOLUTION.
- SIMPLIFIED IMAGE ANALYSIS.
- HIGH THROUGHPUT.
- OLIGO STRATEGY ALLOWS GENOME BASED DESIGN.

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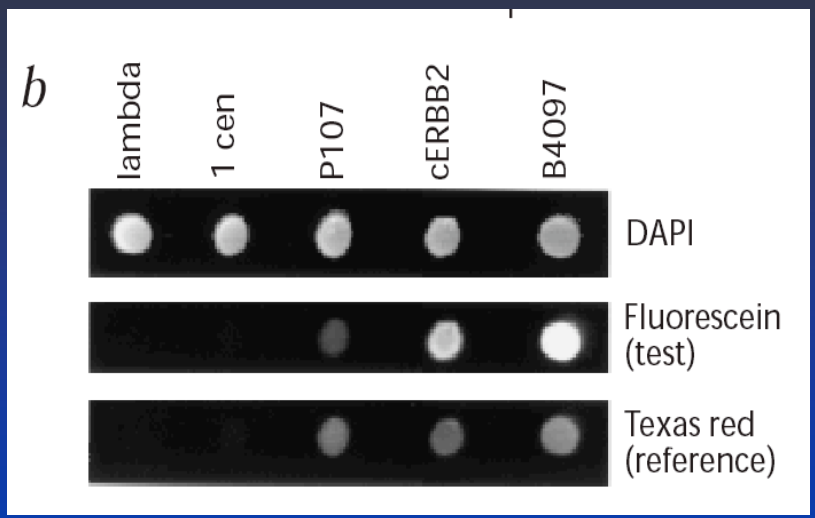
Cancer Genetics Branch

CGH BAC ARRAYS

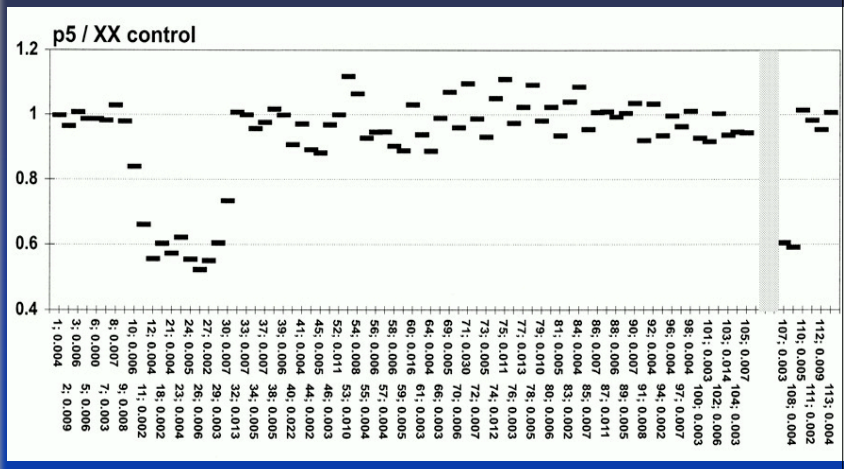


Pinkel D et al., Nature Genetics 20, 207 - 211 ,1998.

National Human Genome Research Institute

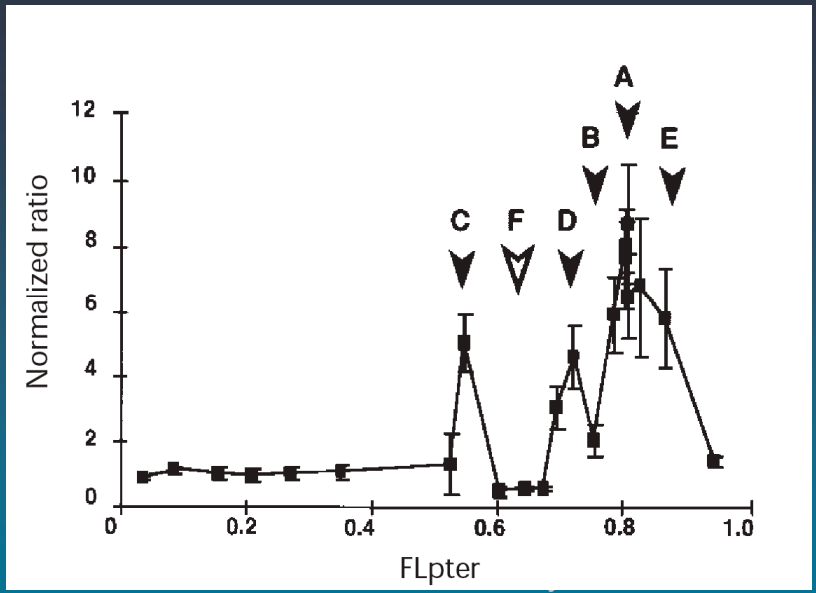
Cancer Genetics Branch

CGH BAC ARRAYS



Bruder CE et al., Hum Mol Genet. 2001;10:271-82.

Cancer Genetics Branch

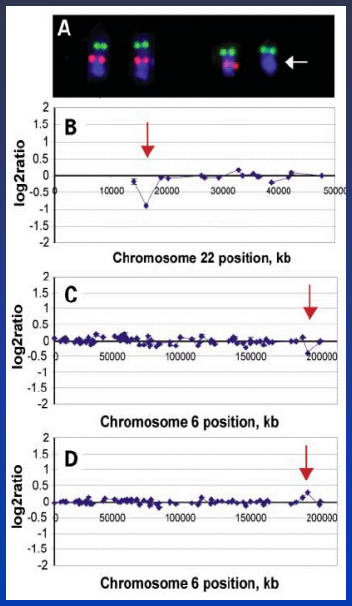


Pinkel et al. Nat Gen 20:207

National Human Genome Research Institute

Cancer Genetics Branch

CGH BAC ARRAYS



Albertson and Pinkel Hum Mol Genet 2003 12:145

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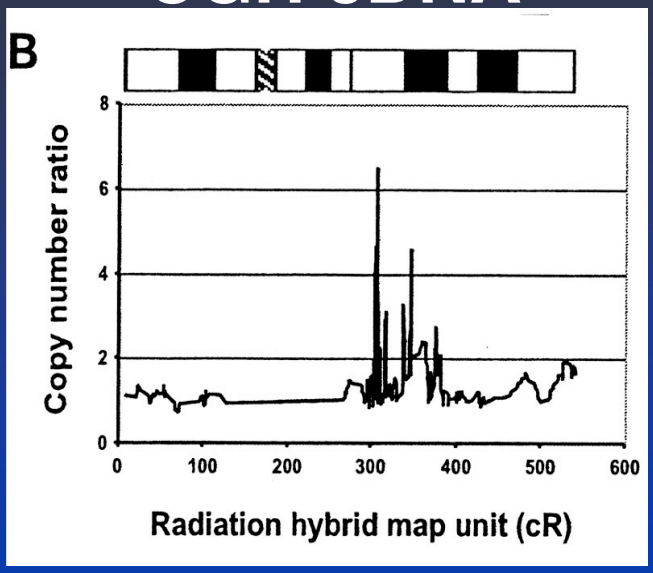
Cancer Genetics Branch

CGH cDNA



Kauraniemi P et al., Cancer Res. 2001 ;61:8235-40.

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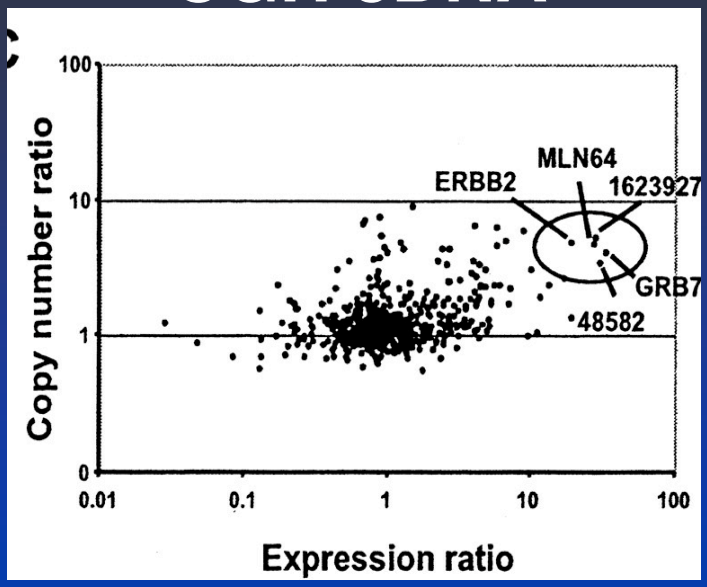
Cancer Genetics Branch

CGH cDNA

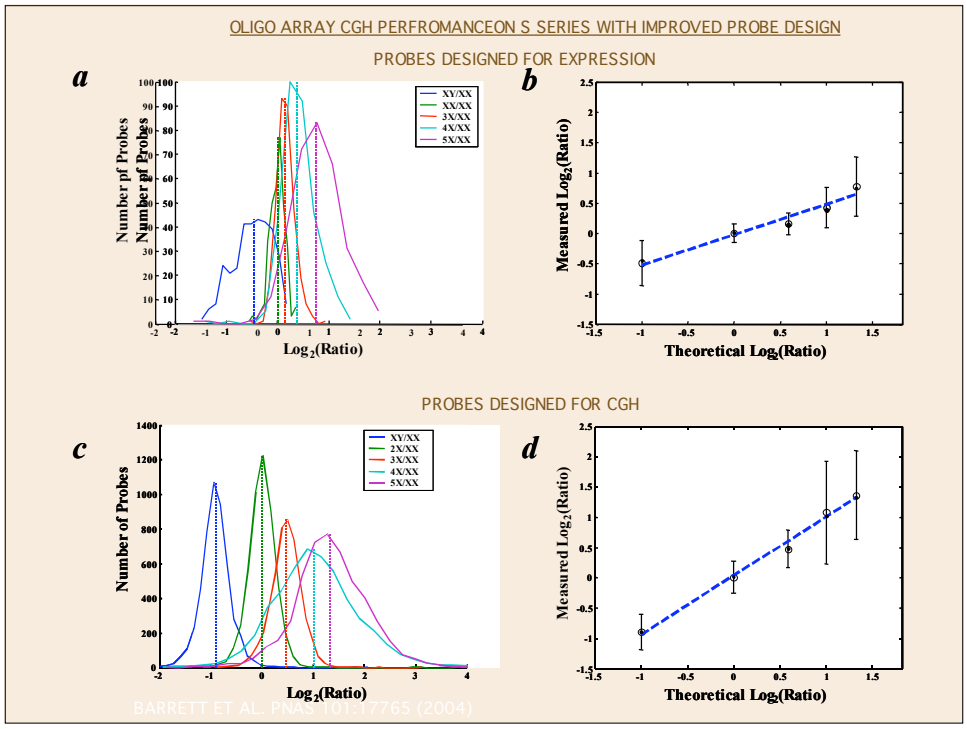


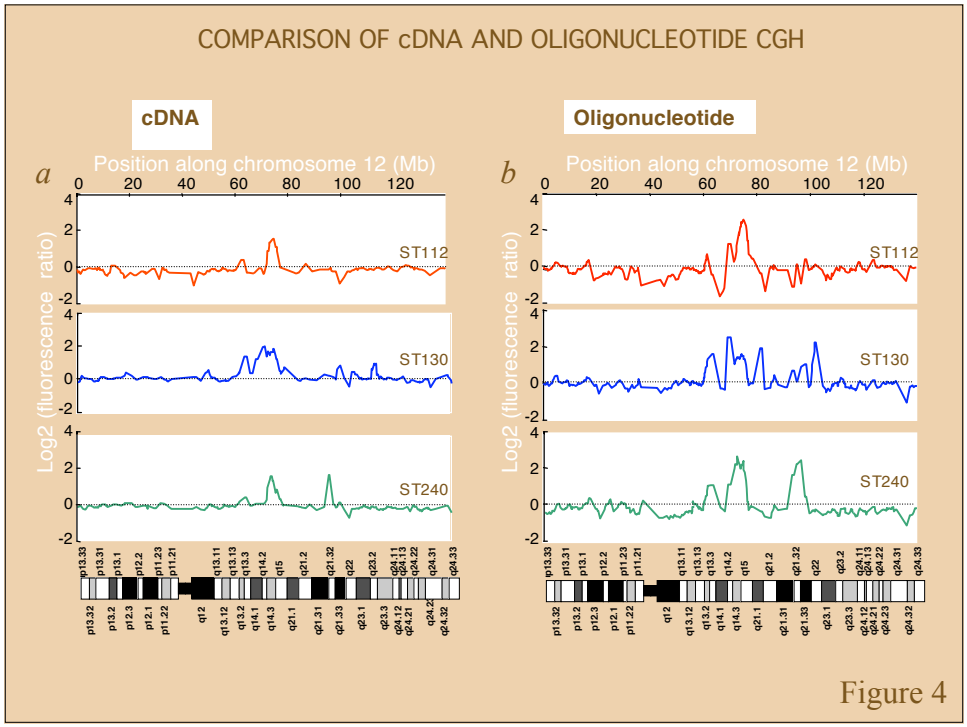
Kauraniemi P et al., Cancer Res. 2001, 61:8235-40

Cancer Genetics Branch

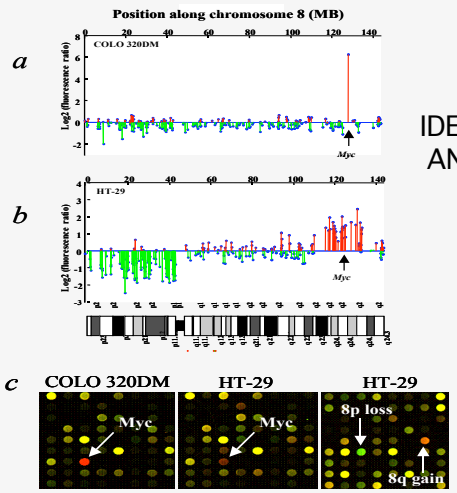
OLIGONUCLEOTIDE BASED CGH

- No bacterial cultures.
- Flexible in silico design.
- Resolution limited only by feature density
- Challenge: complex hybridization


OLIGO ARRAY CGH PERFROMANCEON S SERIES WITH IMPROVED PROBE DESIGN
PROBES DESIGNED FOR EXPRESSION
a
Number pf Probes
Log2(Ratio)
XY/XX
XX/XX
3X/XX
4X/XX
5X/XX
b
Measured Log2(Ratio)
Theoretical Log2(Ratio)
PROBES DESIGNED FOR CGH
c
Number of Probes
Log2(Ratio)
XY/XX
2X/XX
3X/XX
4X/XX
5X/XX
d
Measured Log2(Ratio)
Theoretical Log2(Ratio)
BARRETT ET AL. PNAS 101:17765 (2004)


COMPARISON OF cDNA AND OLIGONUCLEOTIDE CGH
cDNA
Oligonucleotide
a
b
Position along chromosome 12 (Mb)
Log2 (fluorescence ratio)
ST112
ST130
ST240
Figure 4

Cancer Genetics Branch



IDENTIFICATION OF GAINS AND LOSSES IN CANCER CELLS

Figure 1. Barrett et al.

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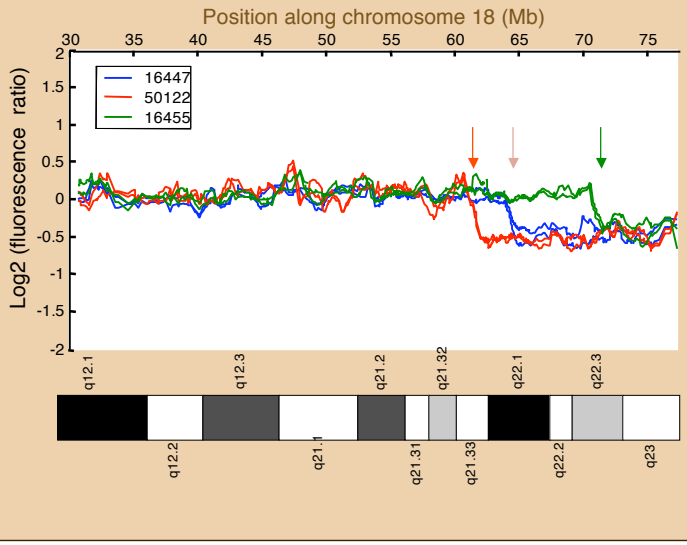
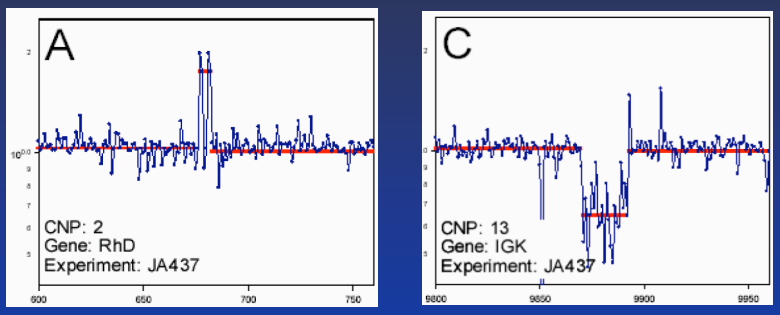
LOCATING CONSTITUTIONAL DELETIONS



Cancer Genetics Branch

HIGH DENSITY OLIGO ARRAYS FOR DETECTING COPY NUMBER POLYMORPHISM



Sebat et al., Science 2004;305:525.

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Cancer Genetics Branch

DNA Microarray Applications

- Resequencing
- Comparative Genomic Hybridization
- **Gene Expression**
- Transcription factor localization
- Chromatin/DNA modification

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Gene Expression ProfilingTechnologies

- cDNA library sequencing
- Serial analysis of gene expression (SAGE)
- MPSS (massively parallel signature sequencing)
- **Microarray hybridization**

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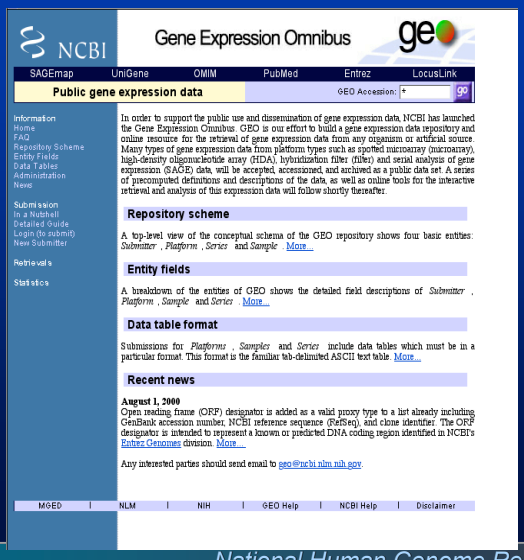
Cancer Genetics Branch

Accessing Expression Data

- Individual Lab and Journal Sites



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Accessing Expression Data

Cancer Genetics Branch

Publishing Expression Data

•MIAME standard

Minimum Information about a Microarray Experiment

Format required by many journals

Cancer Genetics Branch

STRATEGIES FOR SIGNAL GENERATION FROM mRNA

- Fluorochrome conjugated cDNA
- Ligand substituted nucleotides with secondary detection (e.g. biotin-streptavidin)
- Radioactivity
- RNA amplification

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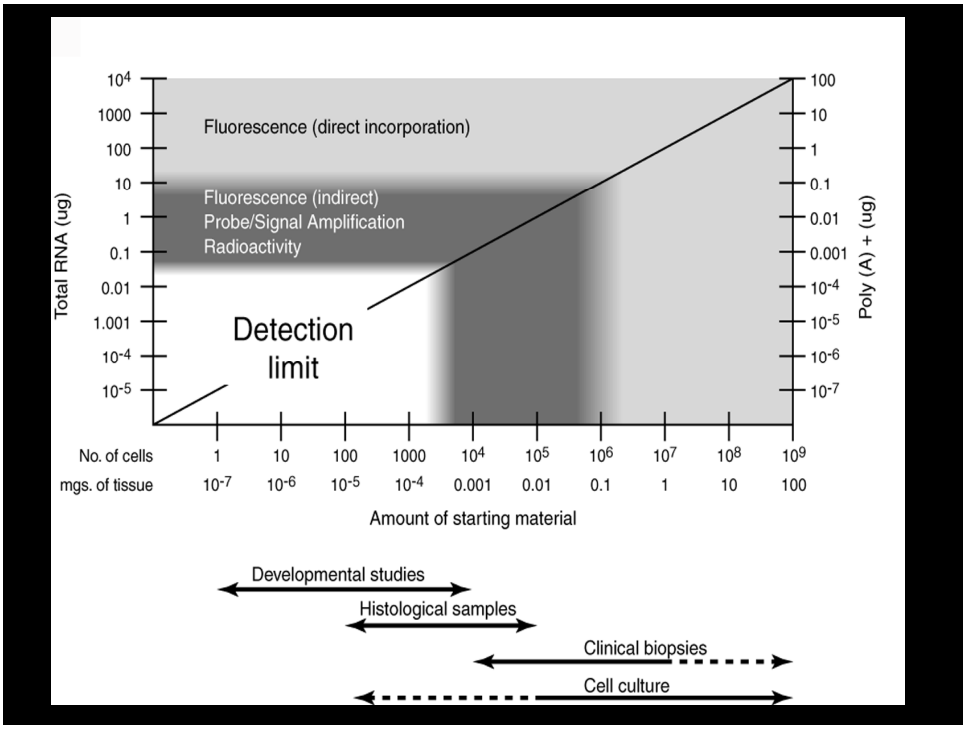
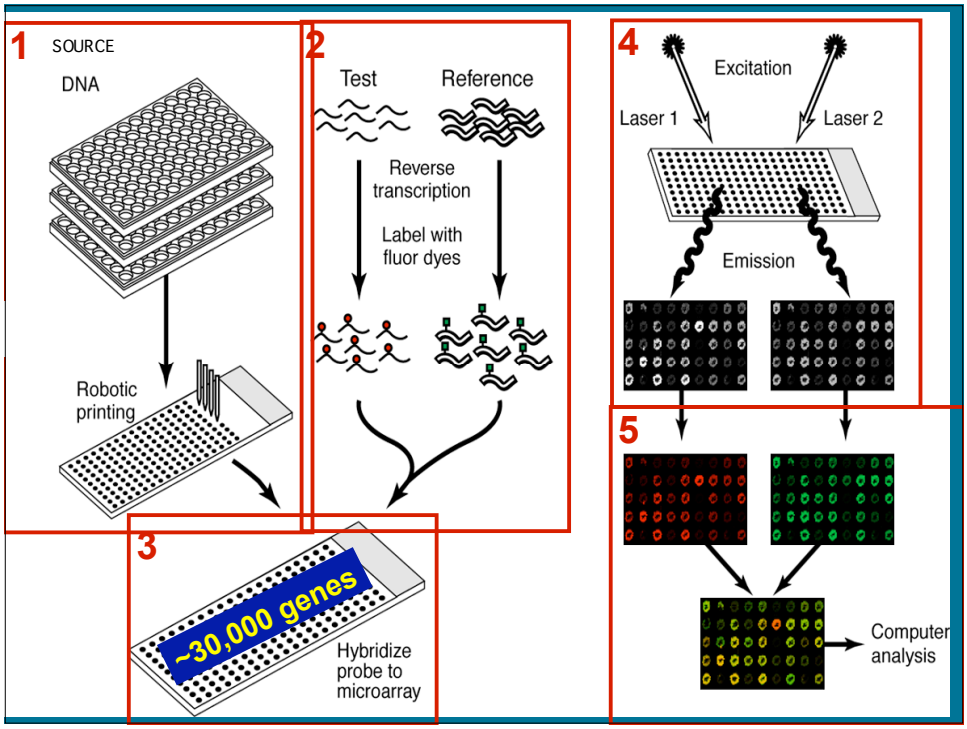
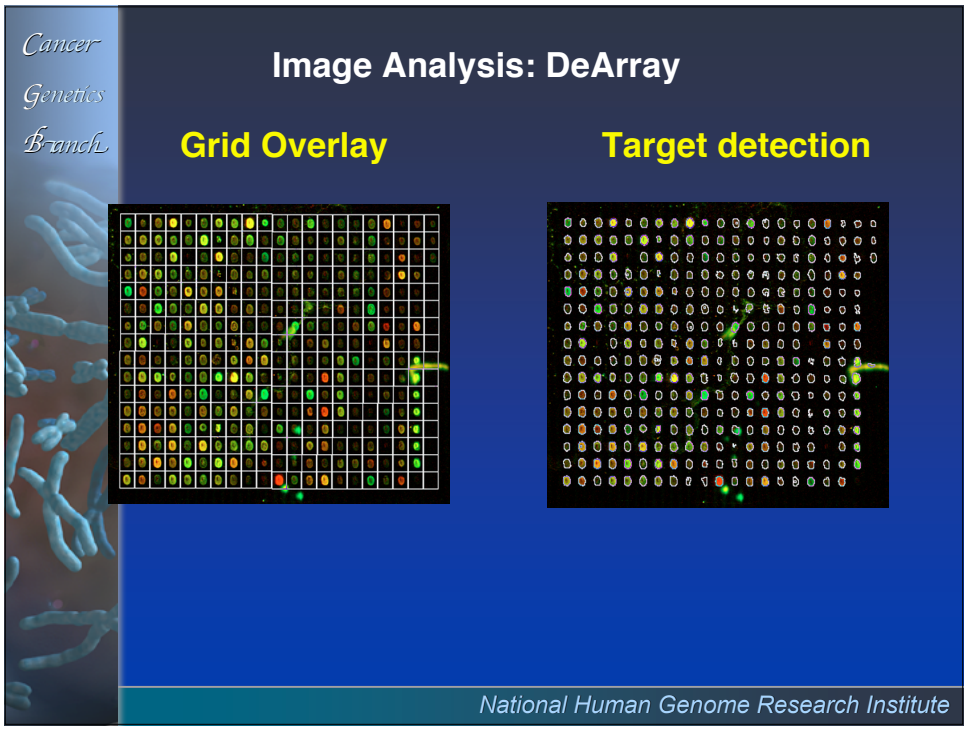
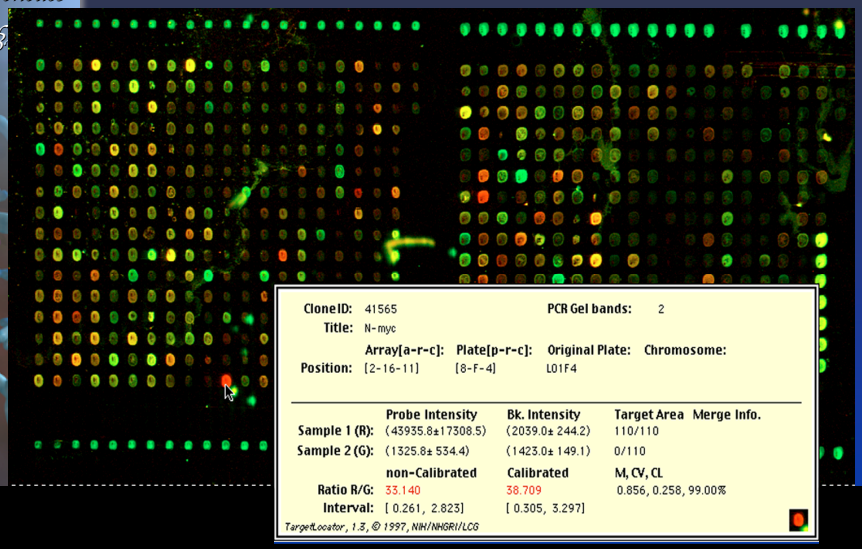



1
SOURCE
DNA
Robotic printing
2
Test
Reference
Reverse transcription
Label with fluor dyes
3
~30,000 genes
Hybridize probe to microarray
4
Excitation
Laser 1
Laser 2
Emission
5
Computer analysis


Cancer Genetics Branch
Image Analysis: DeArray
Grid Overlay
Target detection
National Human Genome Research Institute

Cancer Genetics Branch

Image Analysis: DeArray



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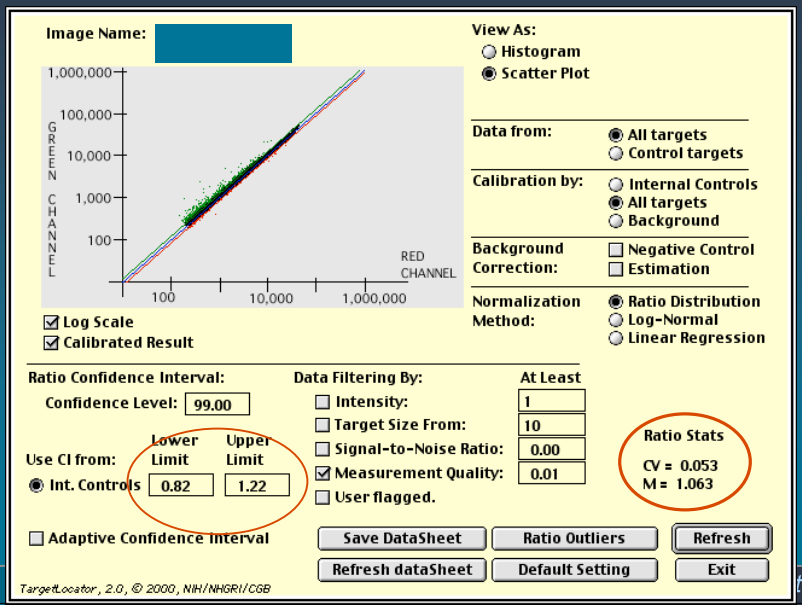
DATA QUALITY IS CRITICAL



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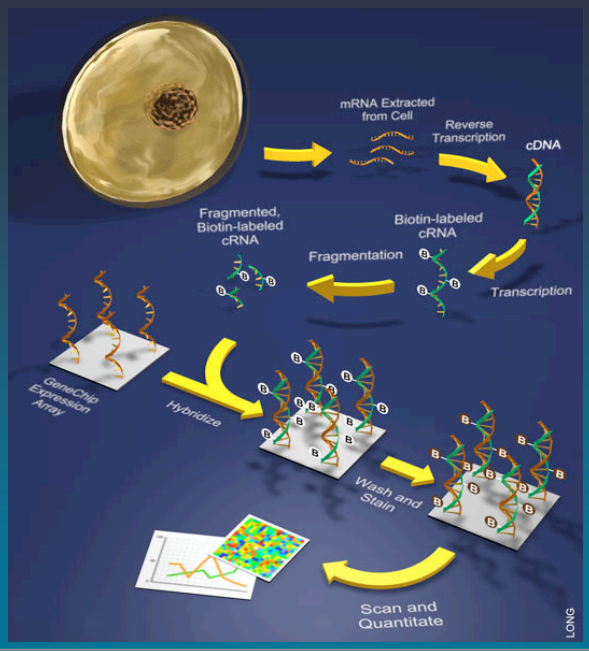

ONE COLOR HYBRIDIZATION ON AN OLIGO ARRAY

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Output of Microarray Analysis:

expression ratio
(2 color hybridization)

or

relative expression level
(1 color hybridization)

Both types of data can be analyzed with essentially the same tools.

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APPLICATIONS OF EXPRESSION ARRAYS

- **Expression profiling**

  Power arises from increasing sample number

- **Direct comparisons (Induction)**

  Biological system critical

- **Genome Annotation**

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A RECURRING PROBLEM

Disease Genes

Transcription factors

Hormones/growth factors

Drugs

Toxins

Infectious agents

Physical agents

?????

Downstream Genes

- **Direct targets**
- **Indirect targets**

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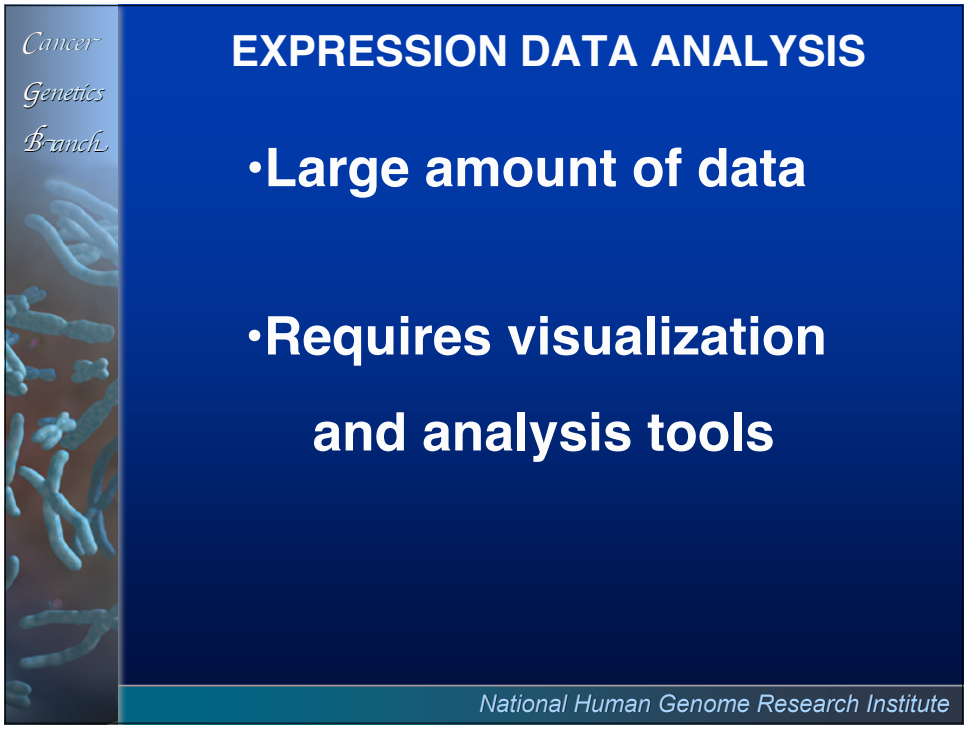
Cancer Genetics Branch
EXPRESSION DATA ANALYSIS
•Large amount of data
•Requires visualization and analysis tools
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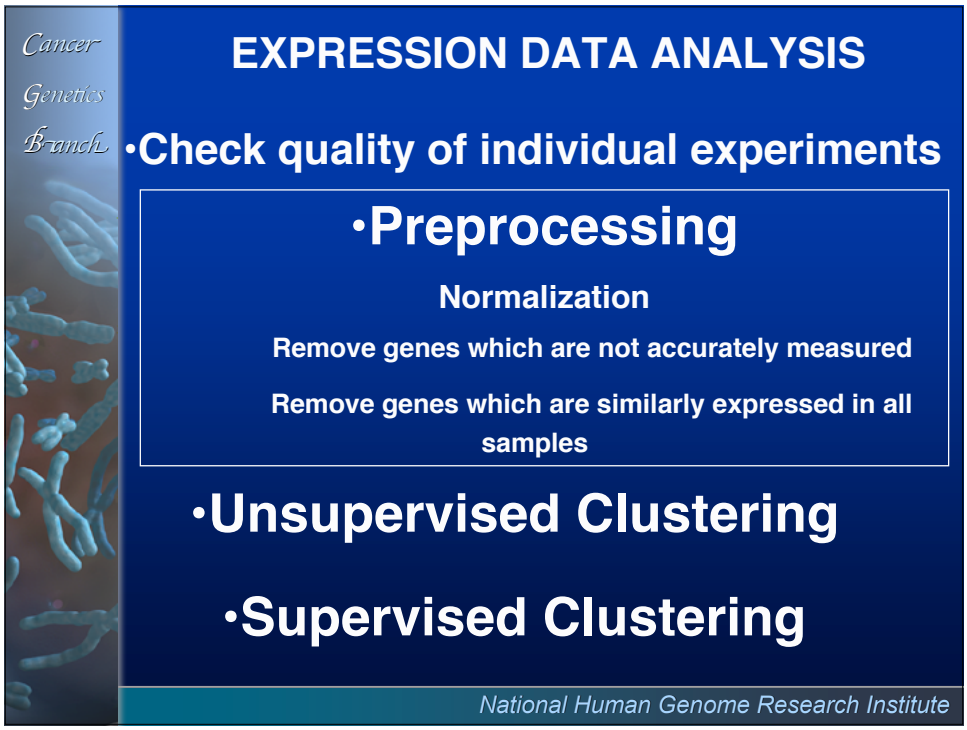
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EXPRESSION DATA ANALYSIS
•Check quality of individual experiments
•Preprocessing
Normalization
Remove genes which are not accurately measured
Remove genes which are similarly expressed in all samples
•Unsupervised Clustering
•Supervised Clustering
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Unsupervised Clustering

How do genes and samples organize into groups?

Powerful method of data display.

Does not prove the validity of groups.

- Clustered Samples Are Biologically Similar
- Clusters of Co-expressed genes
  - May be functionally related
  - May be enriched for pathways

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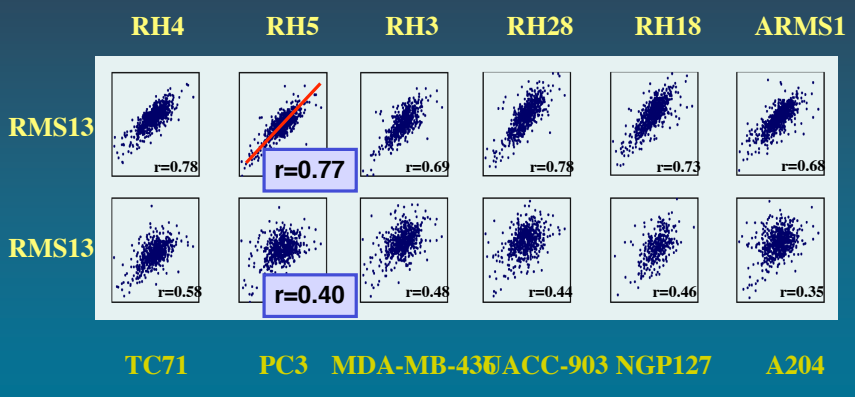
UNSUPERVISED CLUSTERING IS BASED ON A GLOBAL SIMILARITY METRIC



Matrix of Pearson Correlation Coefficients Distance Map

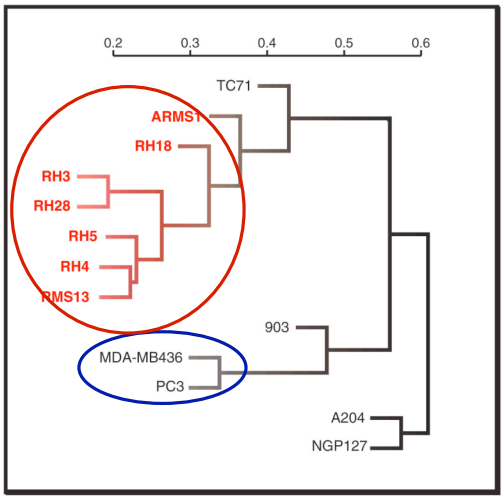
78 pair-wise comparisons

RH28

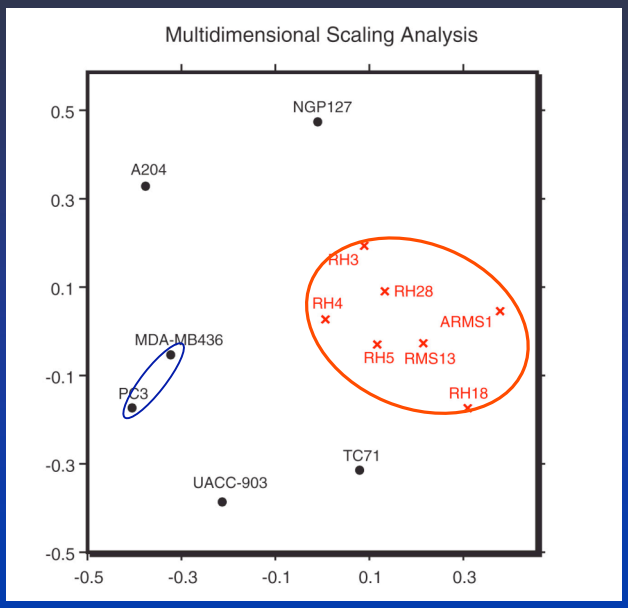
RH3 0.807

	RH3	RH4	RH5	RMS13	RH18	RH28	A204	NGP127	TC71	UACC-903	MDA-MB-436	PC3
ARMS1	0.547	0.606	0.726	0.683	0.634	0.[illegible]	0.307	0.39	0.498	0.426	0.417	0.314
RH3		0.759	0.736	0.69	0.[illegible]	0.807	0.44	0.565	0.566	0.391	0.452	0.403
RH4			0.771	0.778	0.67[illegible]		0.41	0.486	0.558	0.488	0.555	0.476
RH5				0.769	0.667	0.751	0.37	0.486	0.607	0.43	0.532	0.447
RMS13					0.731	0.746	0.35	0.463	0.582	0.446	0.475	0.404
RH18						0.703	0.274	0.281	0.549	0.389	0.405	0.36
RH28							0.417	0.493	0.644	0.479	0.478	0.42
A204								0.426	0.361	0.398	0.368	0.377
NGP127									0.352	0.241	0.371	0.368
TC71										0.46	0.456	0.472
UACC-903											0.507	0.538
MDA-MB-436												0.662
PC3												

Hierarchical Clustering Dendrogram



DATA DISPLAY BY MULTIDIMENSIONAL SCALING



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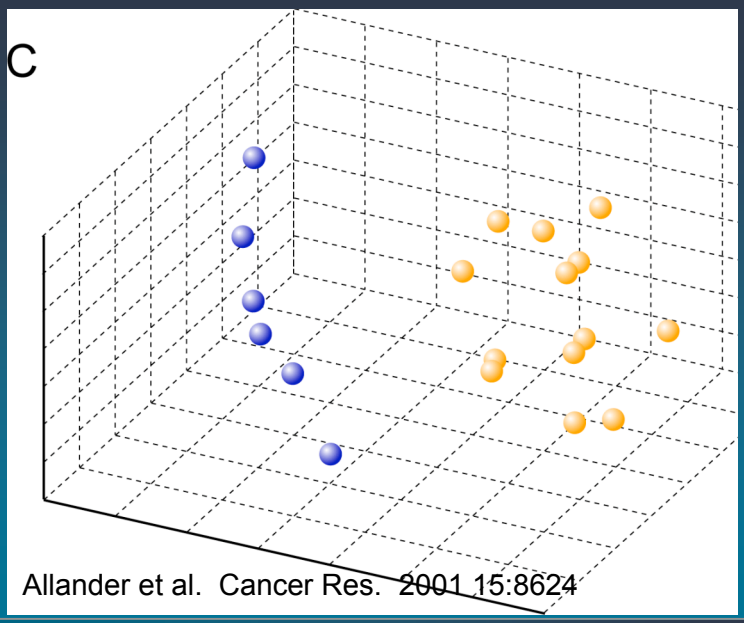
MDS PLOT



Allander et al. Cancer Res. 2001 15:8624

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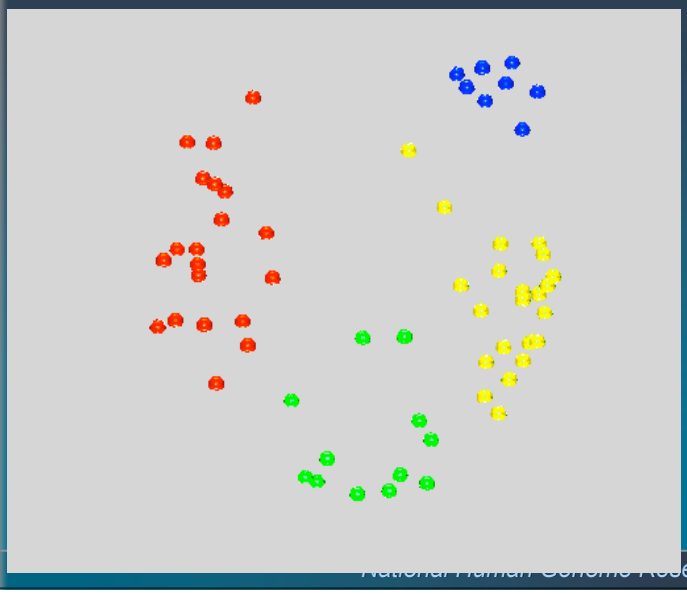
MULTIDIMENSIONAL SCALING



-Lymphoma
RMS
NBL
-EWS

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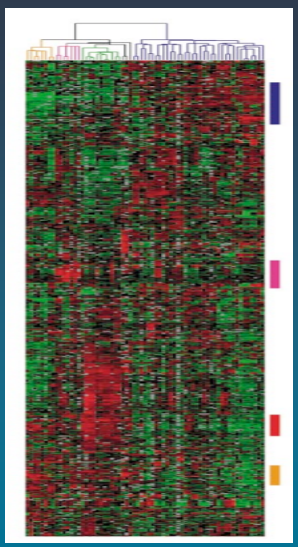
CLUSTERING GENES AND SAMPLES



Perou et al. Nature 2000 406:747

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Supervised Clustering

What genes distinguish samples in selected groups from each other?

- Choice of groups can be based on any known property of the samples.
- Many possible underlying methods: t-test or F-statistic frequently used.
- Output includes ranked gene list.
- Leads to the development of classifiers which can be applied to unknown samples.
- Must address the problem of false discovery due to multiple comparisons and discrepancy between sample/gene numbers.

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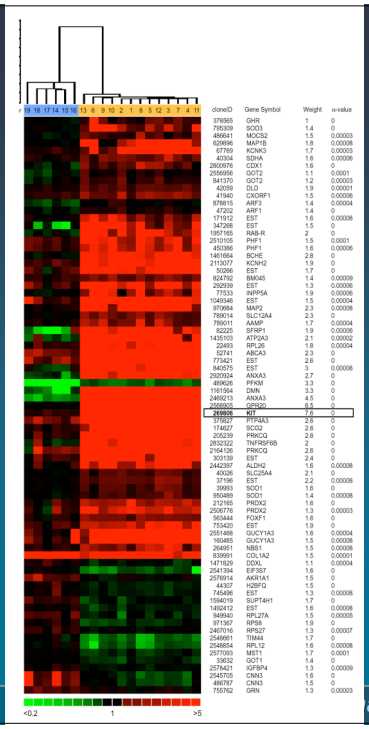

HIERARCHICAL CLUSTERING OF SAMPLES/GENES USING THE GENES SELECTED BY SUPERVISED ANALYSIS

Allander et al. Cancer Res. 2001 15:8624

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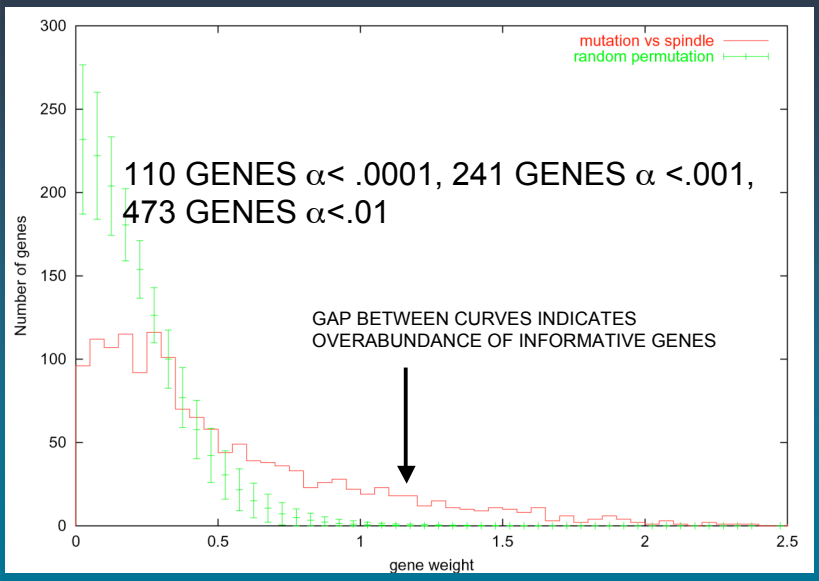
OVERABUNDANCE OF INFORMATIVE GENES DEMONSTRATED BY RANDOM PERMUTATION TEST



Allander et al. Cancer Res. 2001 15:8624

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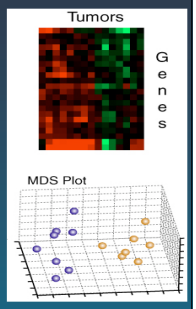
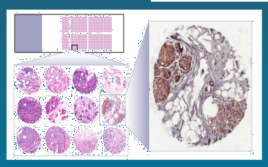
GENOMICS FROM BENCH TO BEDSIDE

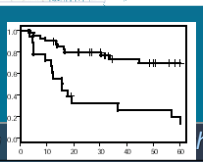
WHOLE GENOME

GENE SELECTION



GENE VALIDATION





ASSAY DEVELOPMENT

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SIGNAL STRENGTH VARIES IN TISSUE PROFILING EXPERIMENTS

THE MOST INTERESTING QUESTIONS TEND TO BE ASSOCIATED WITH WEAKER SIGNAL.

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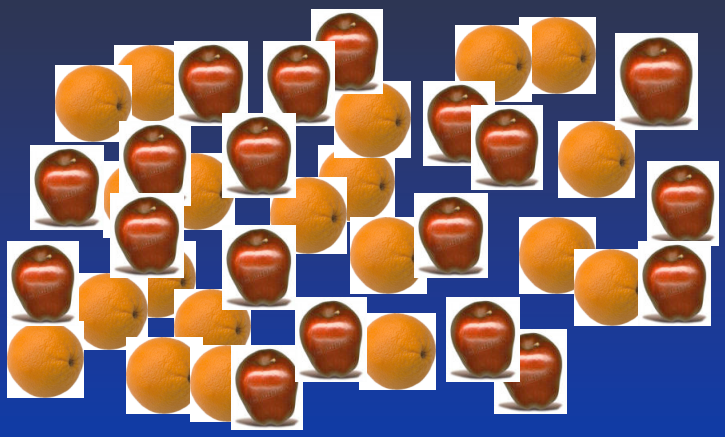
CONSIDER A SAMPLE SET



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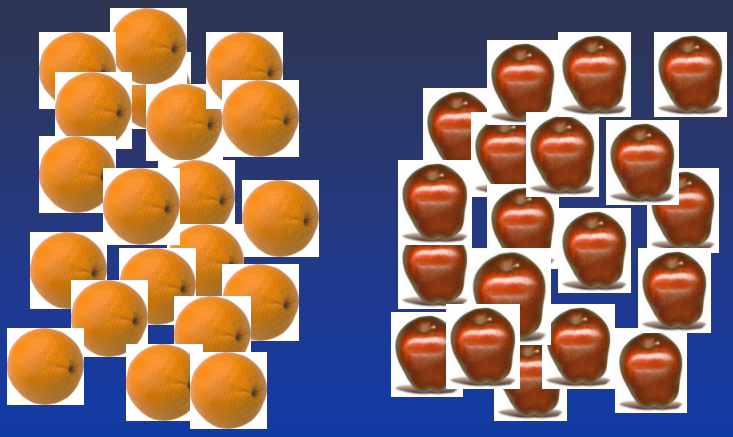
CONSIDER A SAMPLE SET



THESE ARE EASY TO DISTINGUISH BY ONE MEASUREMENT PER INDIVIDUAL.

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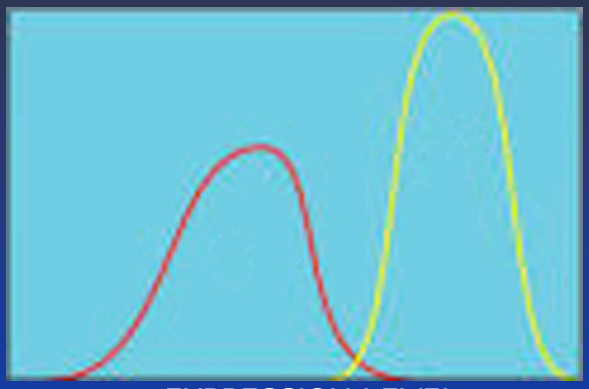
CONSIDER A SAMPLE SET

TUMORS



EXPRESSION LEVEL
(HIGHLY INFORMATIVE GENE)

THESE ARE EASY TO DISTINGUISH BY ONE MEASUREMENT PER INDIVIDUAL.

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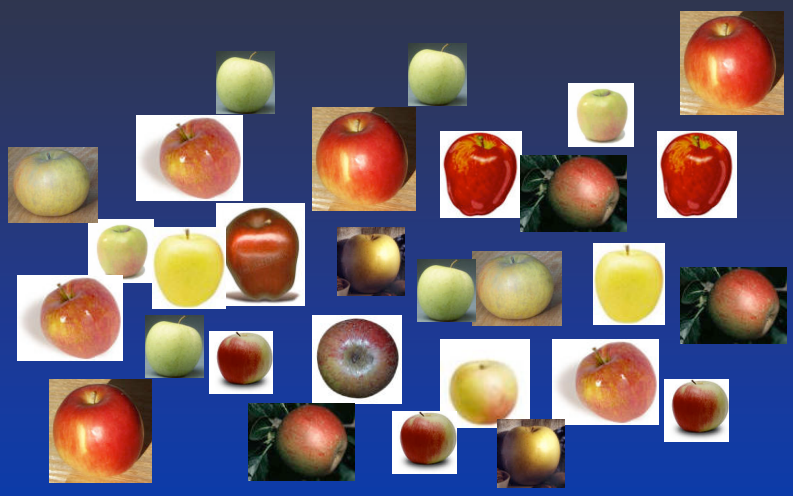
CONSIDER A SAMPLE SET



THESE ARE HARDER TO DISTINGUISH. REQUIRE MORE THAN ONE MEASUREMENT PER INDIVIDUAL.

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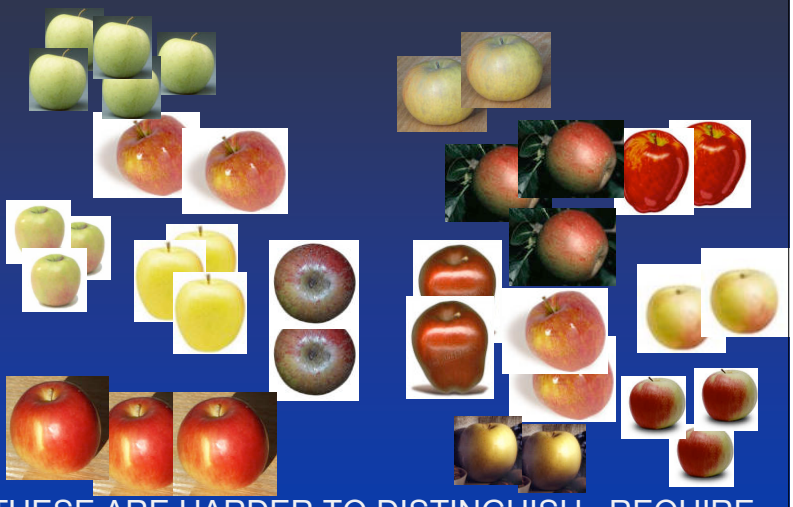
CONSIDER A SAMPLE SET



THESE ARE HARDER TO DISTINGUISH. REQUIRE MORE THAN ONE MEASUREMENT PER INDIVIDUAL.

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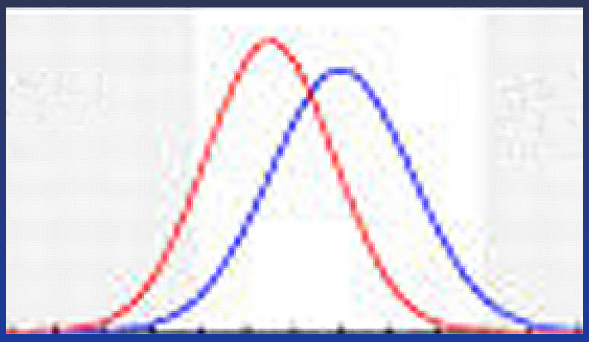
CONSIDER A SAMPLE SET

TUMORS



EXPRESSION LEVEL
(POORLY INFORMATIVE GENE)

THESE ARE HARDER TO DISTINGUISH. REQUIRE MORE THAN ONE MEASUREMENT PER INDIVIDUAL.

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WE CAN TELL APPLES FROM ORANGES.

CAN WE DISTINGUISH DIFFERENT KINDS OF APPLES?

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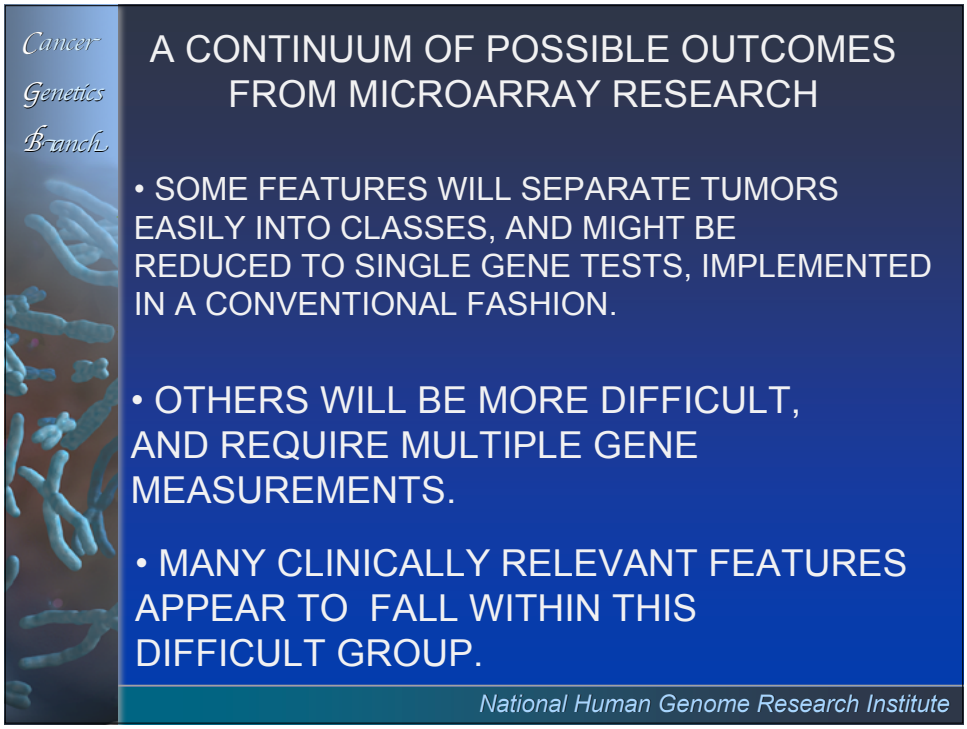
Cancer Genetics Branch
A CONTINUUM OF POSSIBLE OUTCOMES FROM MICROARRAY RESEARCH
• SOME FEATURES WILL SEPARATE TUMORS EASILY INTO CLASSES, AND MIGHT BE REDUCED TO SINGLE GENE TESTS, IMPLEMENTED IN A CONVENTIONAL FASHION.
• OTHERS WILL BE MORE DIFFICULT, AND REQUIRE MULTIPLE GENE MEASUREMENTS.
• MANY CLINICALLY RELEVANT FEATURES APPEAR TO FALL WITHIN THIS DIFFICULT GROUP.
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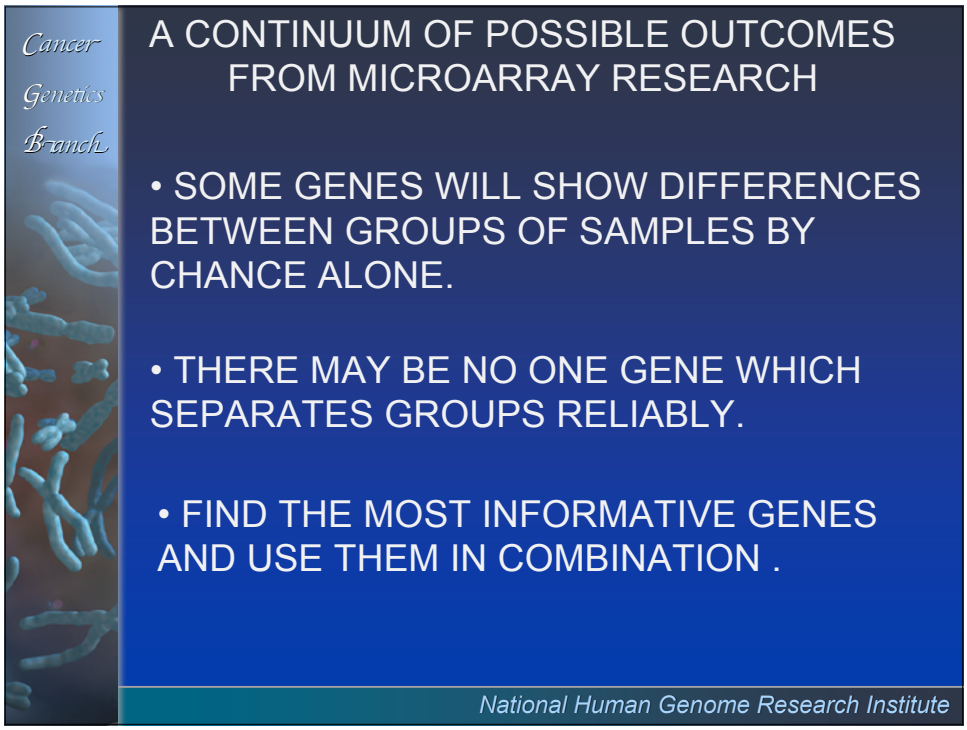
Cancer Genetics Branch
A CONTINUUM OF POSSIBLE OUTCOMES FROM MICROARRAY RESEARCH
• SOME GENES WILL SHOW DIFFERENCES BETWEEN GROUPS OF SAMPLES BY CHANCE ALONE.
• THERE MAY BE NO ONE GENE WHICH SEPARATES GROUPS RELIABLY.
• FIND THE MOST INFORMATIVE GENES AND USE THEM IN COMBINATION .
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RISK OF OVERFITTING IN CLINICAL STUDIES WITH SMALL SAMPLE SETS

NEED INDEPENDENT VALIDATION SETS.

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MICROARRAY STUDIES GENERATE ORGANIZED LIST OF GENES

- Often cryptic and hard to interpret.
- Hypothesis generating, but this is often rather subjective.
- Seldom provide strong evidence for a specific mechanism.
- Expression data is intrinsically limited.

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GETTING BEYOND GENE LISTS

- Optimal use of gene annotations.
- Optimizing use of public data.
- Incorporating data from model systems.
- Linking expression data to sequence.
- Adding other types of genome scale data.

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WHAT SHOULD YOU LOOK FOR IN A CLINICAL MICROARRAY STUDY?

ARE MICROARRAY TECHNOLOGIES READY TO BE IMPLEMENTED IN CLINICAL PRACTICE?

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WHAT TO LOOK FOR IN CLINICAL CORRELATIVE STUDIES USING MICROARRAYS

- WELL DEFINED QUESTION AND PATIENT SAMPLE.
- HIGH QUALITY ARRAY MEASUREMENTS (HARD TO ASSESS WITHOUT REFERENCE TO PRIMARY DATA---SHOULD BE MADE PUBLIC).
- APPROPRIATE AND RIGOROUS STATISTICAL ANALYSIS OF ARRAY DATA.
- FORMAL CLASSIFIER THAT CAN BE APPLIED TO NEW SAMPLES.
- VALIDATION SAMPLE SET.

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WHAT TO LOOK FOR IN CLINICAL CORRELATIVE STUDIES USING MICROARRAYS

- **GOAL SHOULD BE TO SEEK AND VALIDATE CLINICALLY RELEVANT SIGNATURES WITHIN DEFINED PATIENT GROUPS FOR WHICH NO CURRENT FEATURES ADEQUATELY ANSWER THE CLINICAL QUESTION POSED.**

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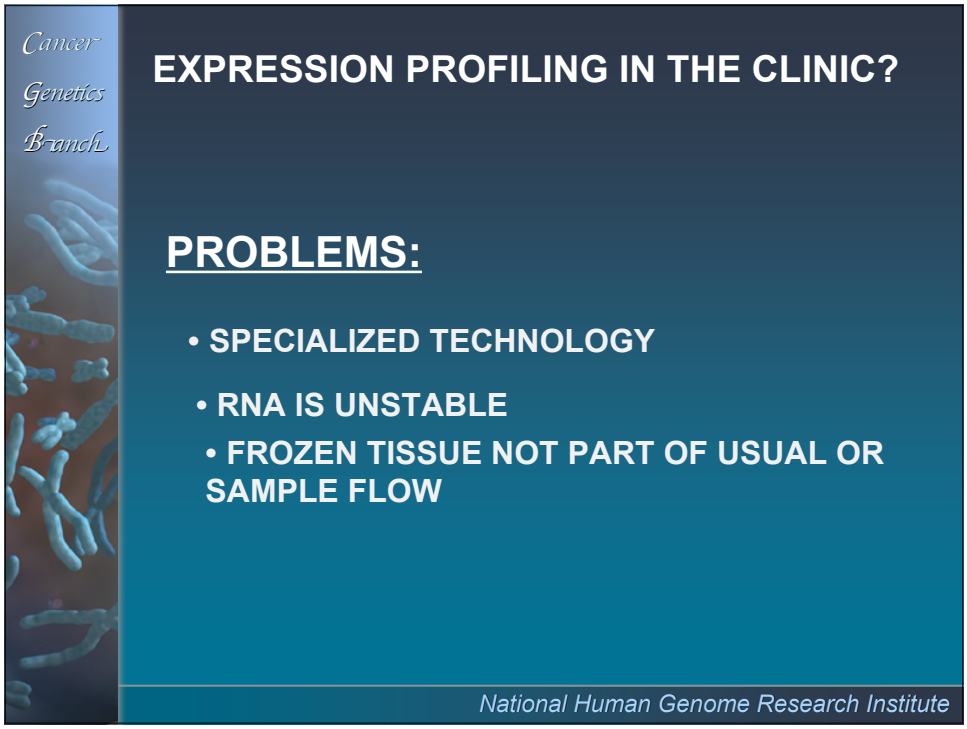
Cancer Genetics Branch
EXPRESSION PROFILING IN THE CLINIC?
PROBLEMS:
• SPECIALIZED TECHNOLOGY
• RNA IS UNSTABLE
• FROZEN TISSUE NOT PART OF USUAL OR SAMPLE FLOW
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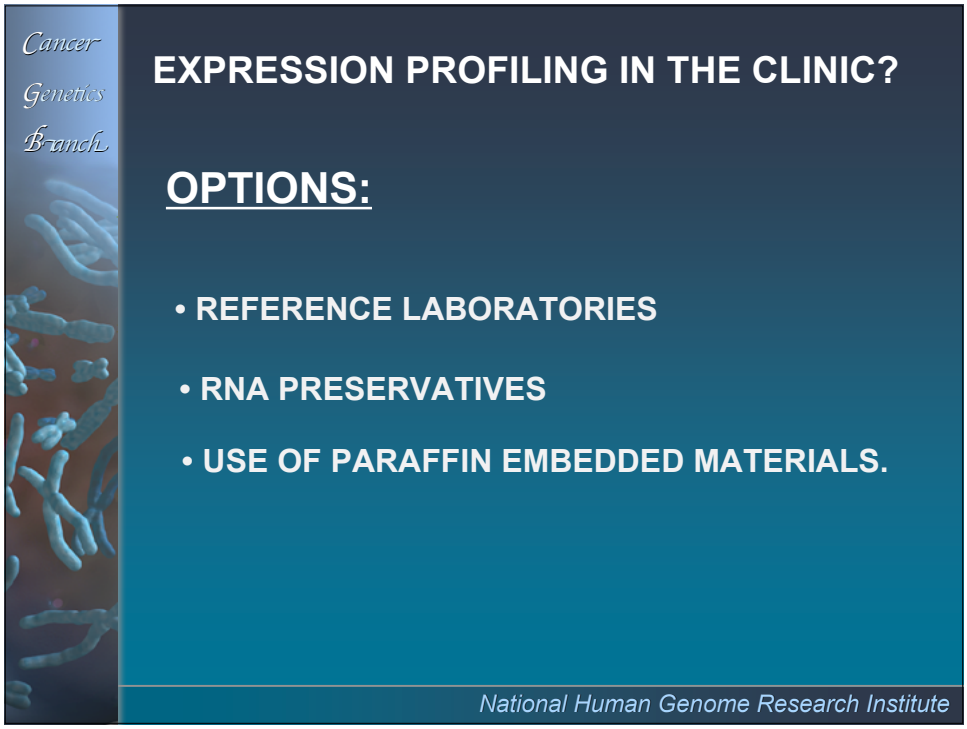
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EXPRESSION PROFILING IN THE CLINIC?
OPTIONS:
• REFERENCE LABORATORIES
• RNA PRESERVATIVES
• USE OF PARAFFIN EMBEDDED MATERIALS.
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EXPRESSION PROFILING IN THE CLINIC?

- COMMERCIAL TESTS BEGINNING TO APPEAR.
- NOT FDA APPROVED
- LIMITED CLINICAL VALIDATION
- ADDITIONAL CLINICAL STUDIES NEEDED

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DNA Microarray Applications

- Resequencing
- Comparative Genomic Hybridization
- Gene Expression
- Transcription factor localization
- Chromatin/DNA modification

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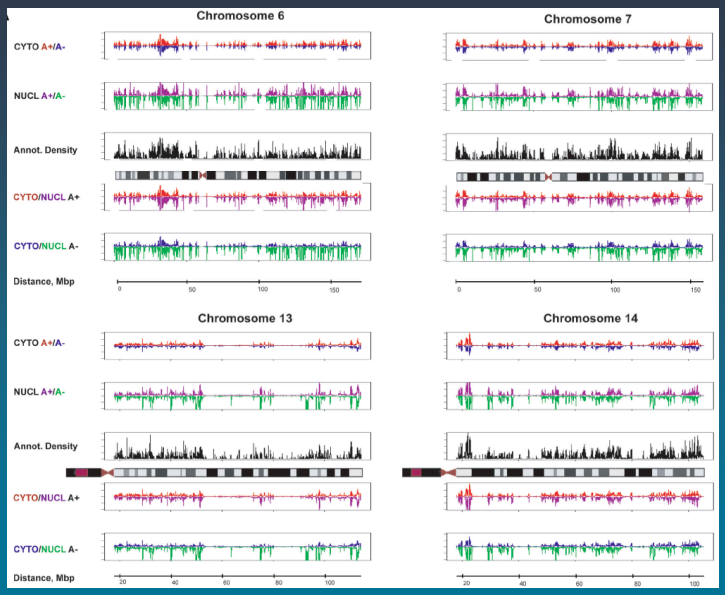
Scanning Chromosomes with Tiling Path Arrays



Cheng et al Science March 29, 2005

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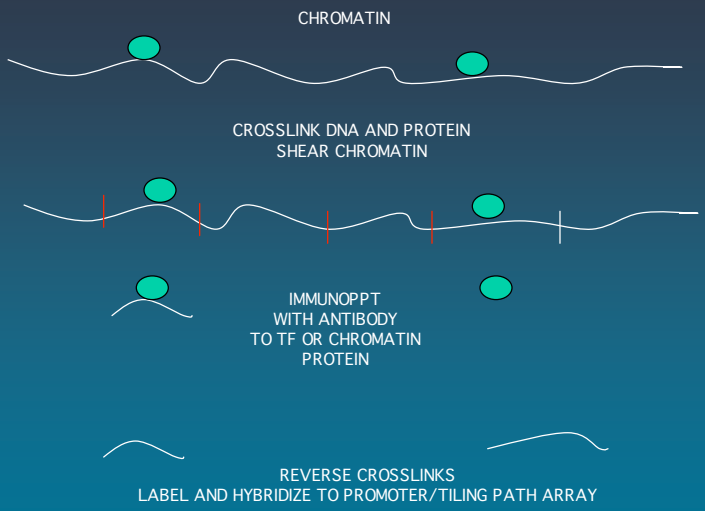
TRANSCRIPTION FACTOR LOCALIZATION ON ARRAYS



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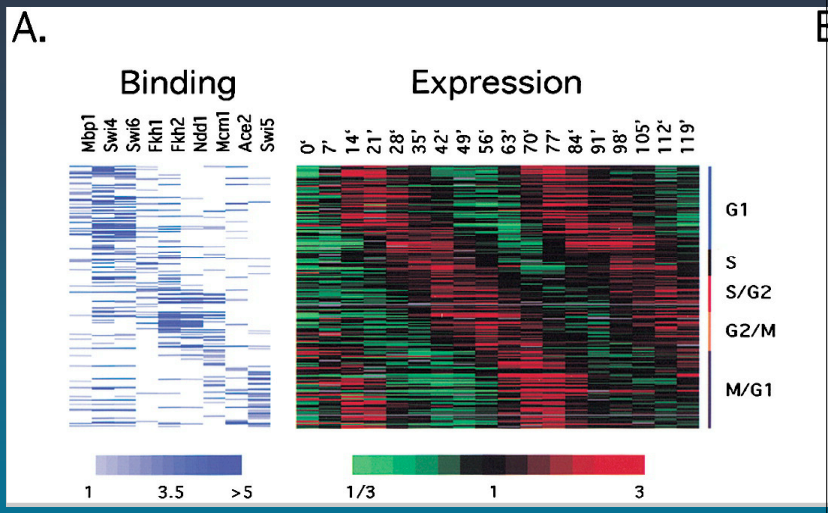
Promoter Occupancy During Yeast Cell Cycle



Simon I Cell. 2001 Sep 21;106(6):697-708

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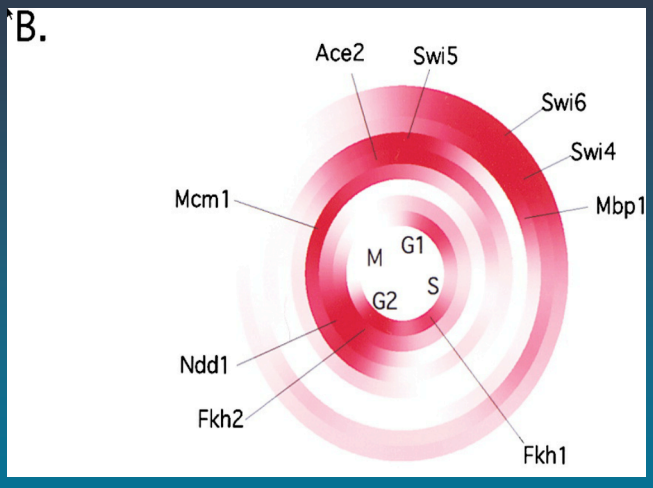
Promoter Occupancy During Yeast Cell Cycle



Simon I Cell. 2001 Sep 21;106(6):697-708.

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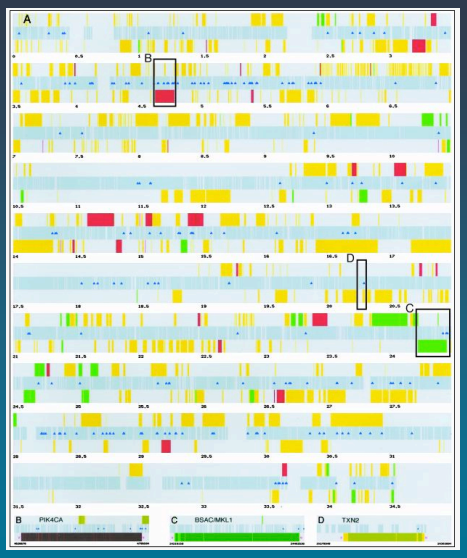
NFKB Binding to Chromosome 22



Martone et al. PNAS. 2004 100:12247.

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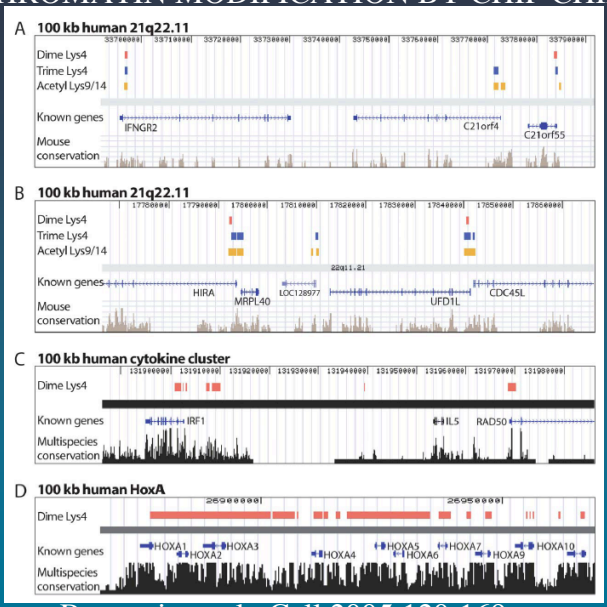
CHROMATIN MODIFICATION BY CHIP CHIP



Bernstein et al. Cell 2005 120:169.

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Access

- Login
- User Registration
- Terms Of Service
- Access Policy
- Disclaimers

Data I/O

- Upload Data
- Annotate Data
- Preprocess Data
- Data Management
- Job Status

Analysis

- Overview
- Visualization
- Clustering
- Time Course Analysis
- Gene Selection
- Classification
- Image Analysis

Resources

- Selected Publications
- Download Programs
- Related Links
- Credits / Contacts
- Help / Support

Version 2.1
Last updated February 2005

National Human Genome Research Institute

CIT Center For Information Technology

If you have any issues or questions please contact us at **support@arrayanalysis.nih.gov**

www.arrayanalysis.nih.gov

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Selected Web Sites for Microarrays

Non-Profit

NHGRI http://research.nhgri.nih.gov/microarray/
- The National Human Genome Research Institute microarray website

MGED http://www.mged.org/
- The Microarray Gene Expression Data (MGED) Society is an international organization of biologists, computer scientists, and data analysts that aims to facilitate the sharing of microarray data generated by functional genomics and proteomics experiments.

NCBI http://ncbi.nih.gov/geo/
- The Gene Expression Omnibus is a gene expression and hybridization array data repository, as well as a curated, online resource for gene expression data browsing, query and retrieval. GEO was the first fully public high-throughput gene expression data repository, and became operational in July 2000.

EBI http://www.ebi.ac.uk/microarray/index.html
- The microarray informatics group at the EBI addresses the problem(s) of managing, storing and analyzing microarray data.

TIGR http://www.tigr.org/tdb/microarray/
- The Institute for Genomic Research

Academic

Stanford http://cmgm.stanford.edu/pbrown/mguide/
- The Brown Lab's complete guide to microarraying for the molecular biologist.

Stanford http://genome-www5.stanford.edu/MicroArray/SMD/
- The Stanford microarray database

UCSF http://www.microarrays.org/index.html
- A public source for microarray protocols and software.

MIT http://www-genome.wi.mit.edu/cancer/
- Focuses on genomic and computational solutions to problems in cancer biology and cancer medicine.

National Human Genome Research Institute