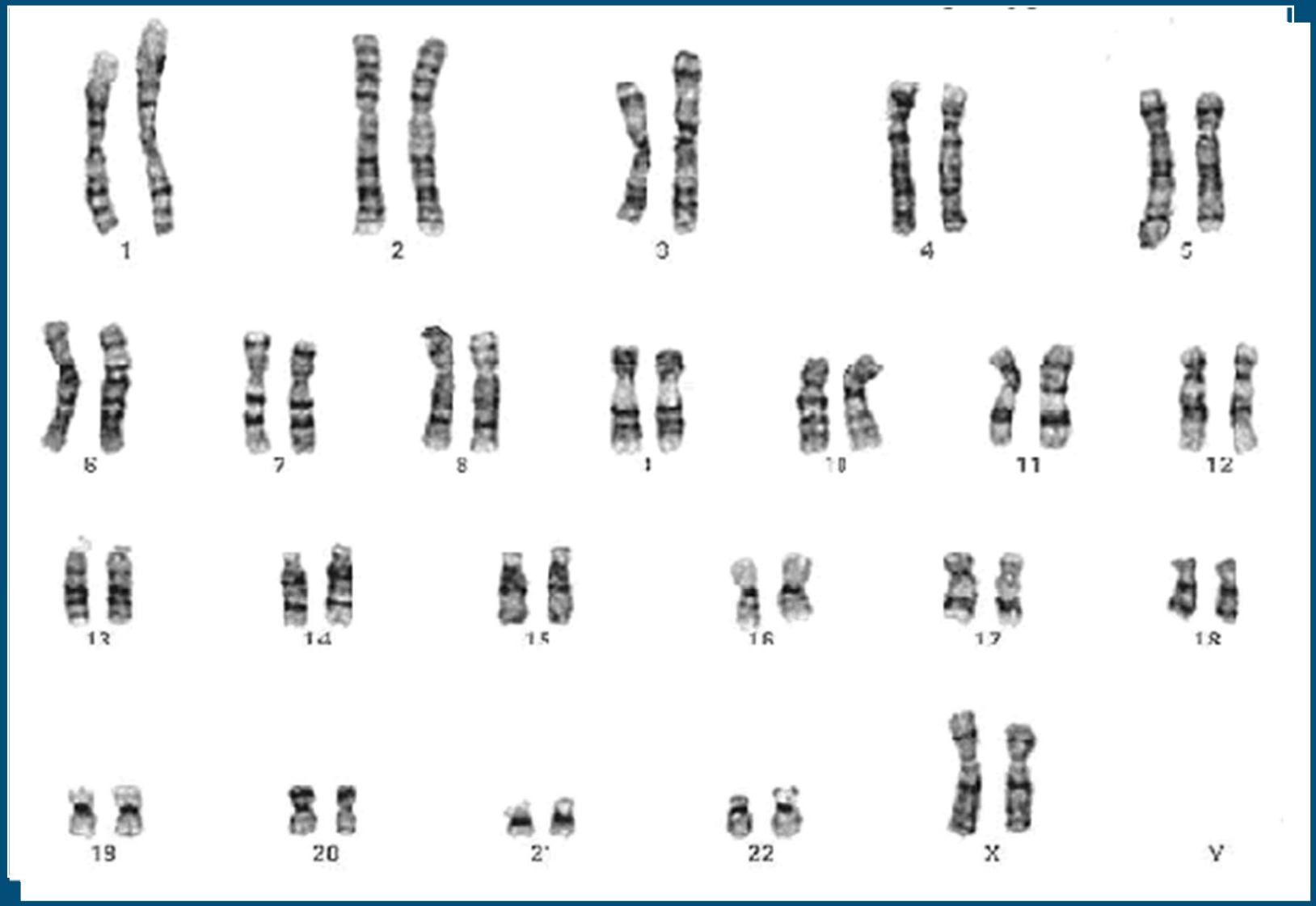
National Cancer Institute

Center for Cancer Research

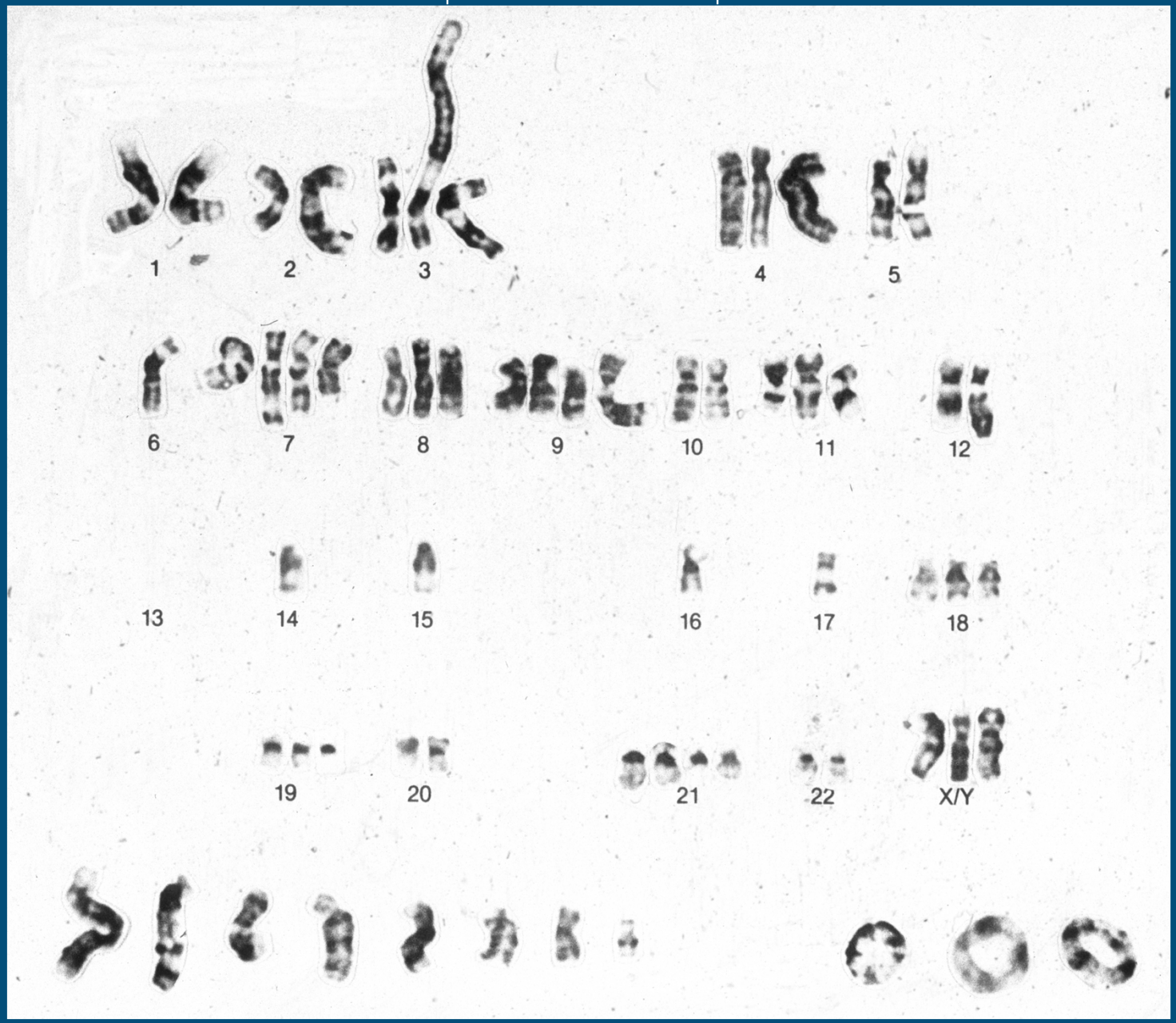
Center for Cancer Research Genomics Initiatives

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

NORMAL ♀



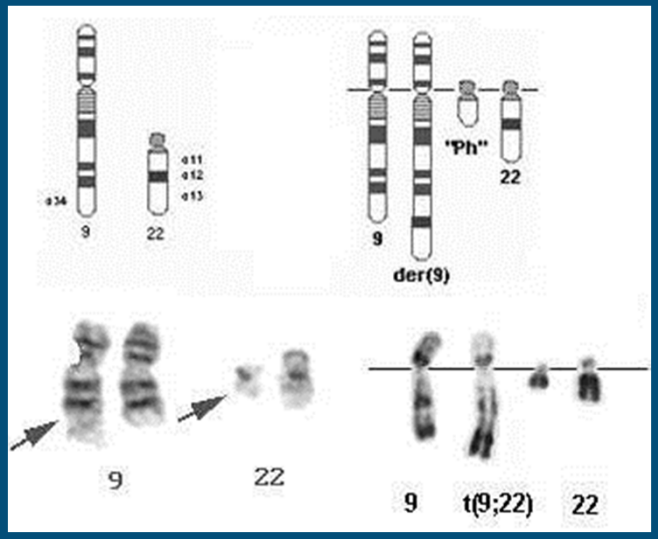
┼ CANCER ┼



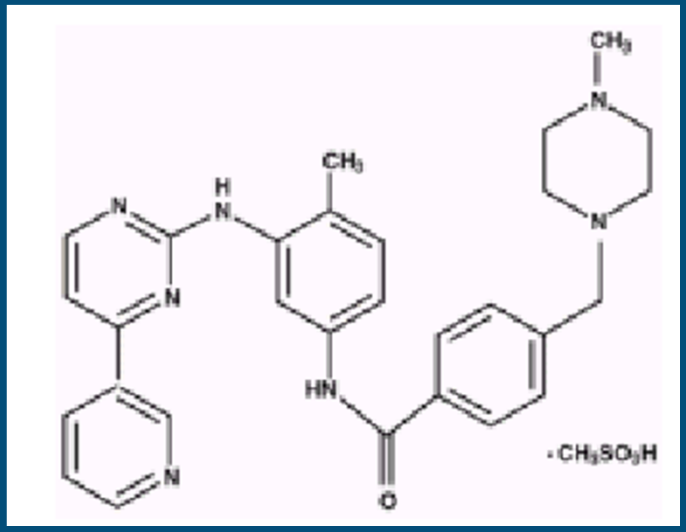
CANCER IS A DISEASE OF DISORDERED GENOME FUNCTION

HIDDEN WITHIN THE CHAOS ARE THE DRIVERS OF CANCER PROGRESSION WHICH CAN POTENTIALLY BE TARGETED THERAPEUTICALLY.

WHY INVESTIGATE THE CANCER GENOME?



Nowell and Hungerford 1960



Gleevec (imatinib) 1996

WHAT IS WRONG WITH THE CANCER GENOME?

- POINT MUTATIONS
- METHYLATION ABNORMALITIES
- CHROMOSOME TRANSLOCATIONS
- COPY NUMBER CHANGES

THESE CHANGES AT THE DNA LEVEL RESULT IN HIGHLY ABNORMAL GENOME FUNCTION.

APPROACHES TO CANCER GENETICS

- IDENTIFY INHERITED VARIANTS IN THE GENOME THAT INCREASE CANCER RISK:

  GENETIC ASSOCIATION

- IDENTIFY DIFFERENCES BETWEEN THE TUMOR GENOME AND THE

  NORMAL GENOME: TUMOR PROFILING

- INTERACTION BETWEEN THESE TWO APPROACHES REMAINS TO BE EXPLORED.

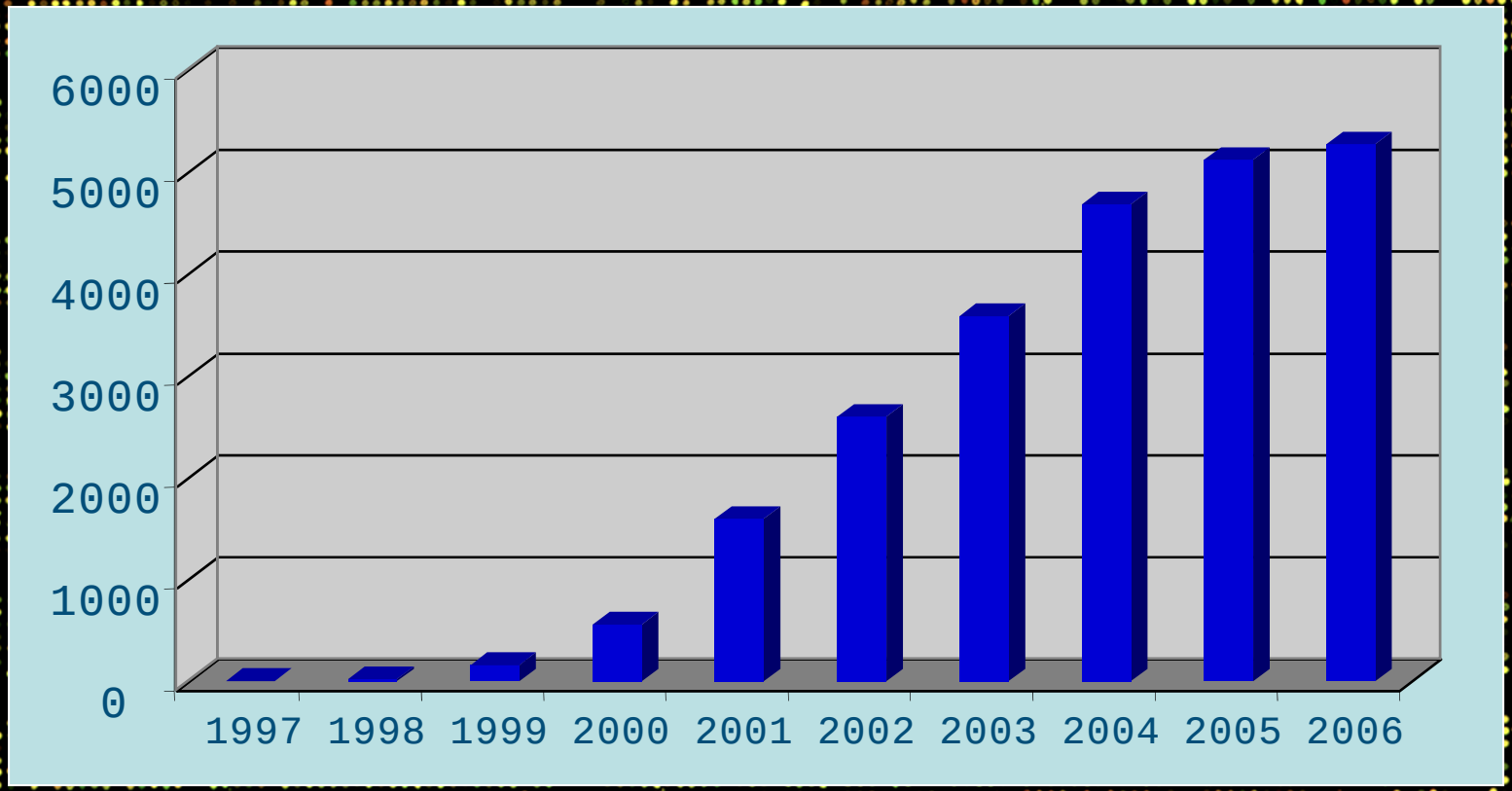
TASKS OF CANCER GENOMICS

DEFINE

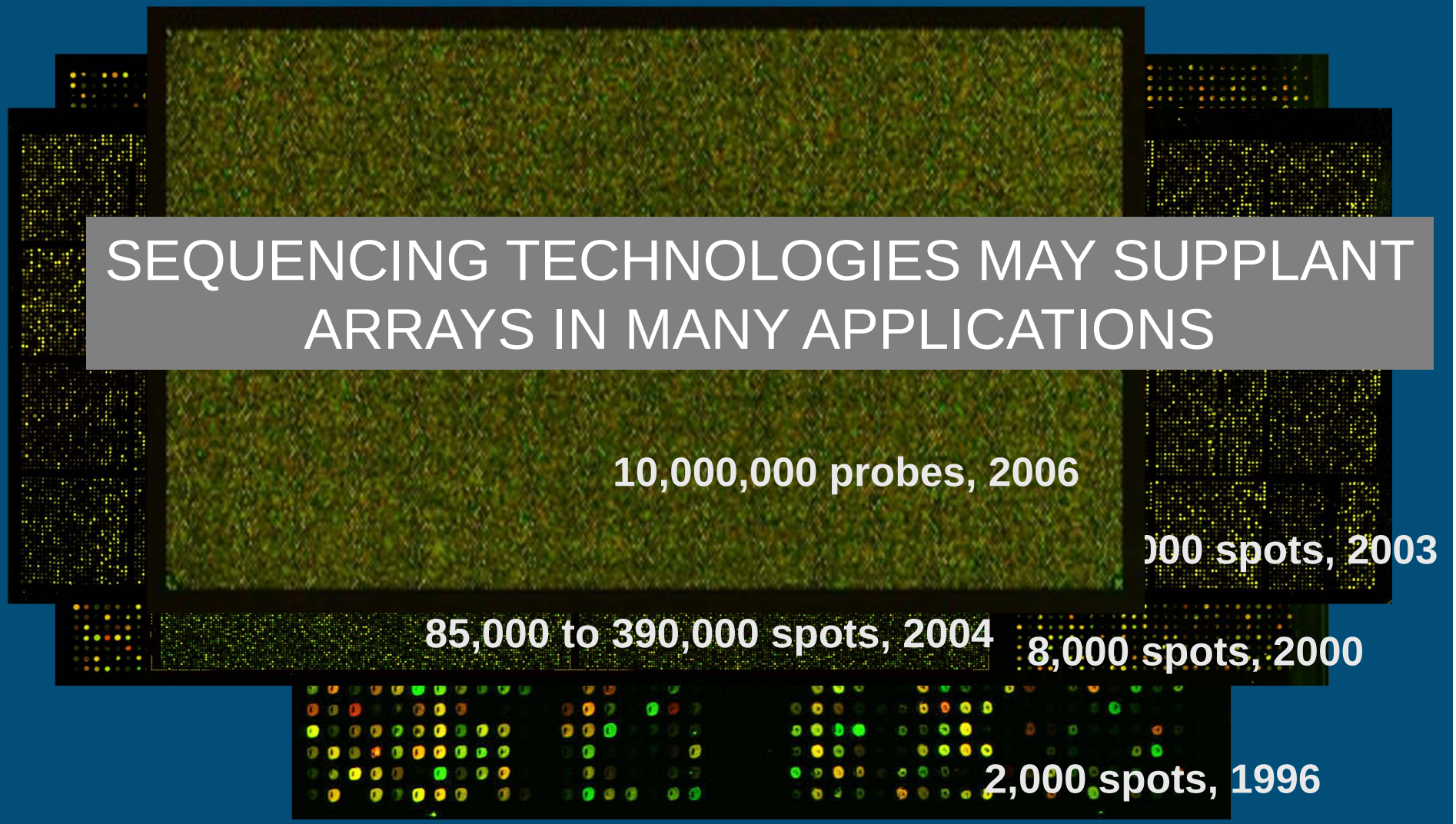
- GENES WHICH ARE TARGETS OF MUTATION
- MECHANISMS OF GENOMIC INSTABILITY.
- PHENOTYPIC CONSEQUENCES.

- TRANSLATE THIS KNOWLEDGE INTO THE CLINICAL ARENA.

PUBMED CITATIONS FOR DNA MICROARRAYS



Microarray Profiling



SCIENTIFIC IMPETUS FOR GENOMICS INITIATIVES IN CCR

- Development of clinically relevant molecular signatures.
- Need to develop predictive biomarkers for targeted therapies.
- Proven implications of tumor genomics for the identification of molecular targets.
- Progress in genome-wide association studies (GWAS) of cancer risk
- Progress in TCGA.
- New and maturing technologies.
- Strong cadre of investigators within CCR.

Center of Excellence in Integrative Cancer Biology and Genomics

Center of Excellence in Integrative Cancer Biology and Genomics

Mission Statement

Promote innovative use of genomics technologies for basic science discoveries and clinical research applications for prevention, diagnosis and treatment of cancer.

Center of Excellence in Integrative Cancer Biology and Genomics

Function and Goals:

I.Strengthen the intramural NCI research program by providing a unique research environment and a capacity to take on “big” high risk projects

II. Enhance collaborative network among the PIs and interactions with other CCR centers, DCEG and programs

III. Consolidate existing cancer databases

IV. Maximize utilization and accessibility of animal models (particularly mouse models)

V. Expand core facilities

VI. Provide a venue for annual meetings with participation from extramural scientists

Center of Excellence in Integrative Cancer Biology and Genomics

Steering Committee

Chair: Snorri Thorgeirsson

Mary Carrington, Elise Kohn, Xin Wang, Stuart Yuspa, Marston Linehan, Curt Harris, Thomas Ried, Glenn Merlino, Beverly Mock, Javed Khan, Richard Simon, Peggy Tucker, Phil Taylor, Stephen Chanock, Louis Staudt, Frank Gonzalez, Paul Meltzer, Scott Durum

Center of Excellence in Integrative Cancer Biology and Genomics

Chair: Snorri S. Thorgeirsson

Enhancing the potential for discovery in the CCR Clinical Program:

Clinical Molecular Profiling Core

Clinical Molecular Profiling Core

CONCEPT:

TO PROVIDE CCR INVESTIGATORS ACCESS TO STATE OF THE ART MOLECULAR PROFILING TECHNOLOGIES FOR BIOSAMPLES COLLECTED IN THE COURSE OF CLINICAL TRIALS

EMPHASIS ON GENOME TECHNOLOGIES

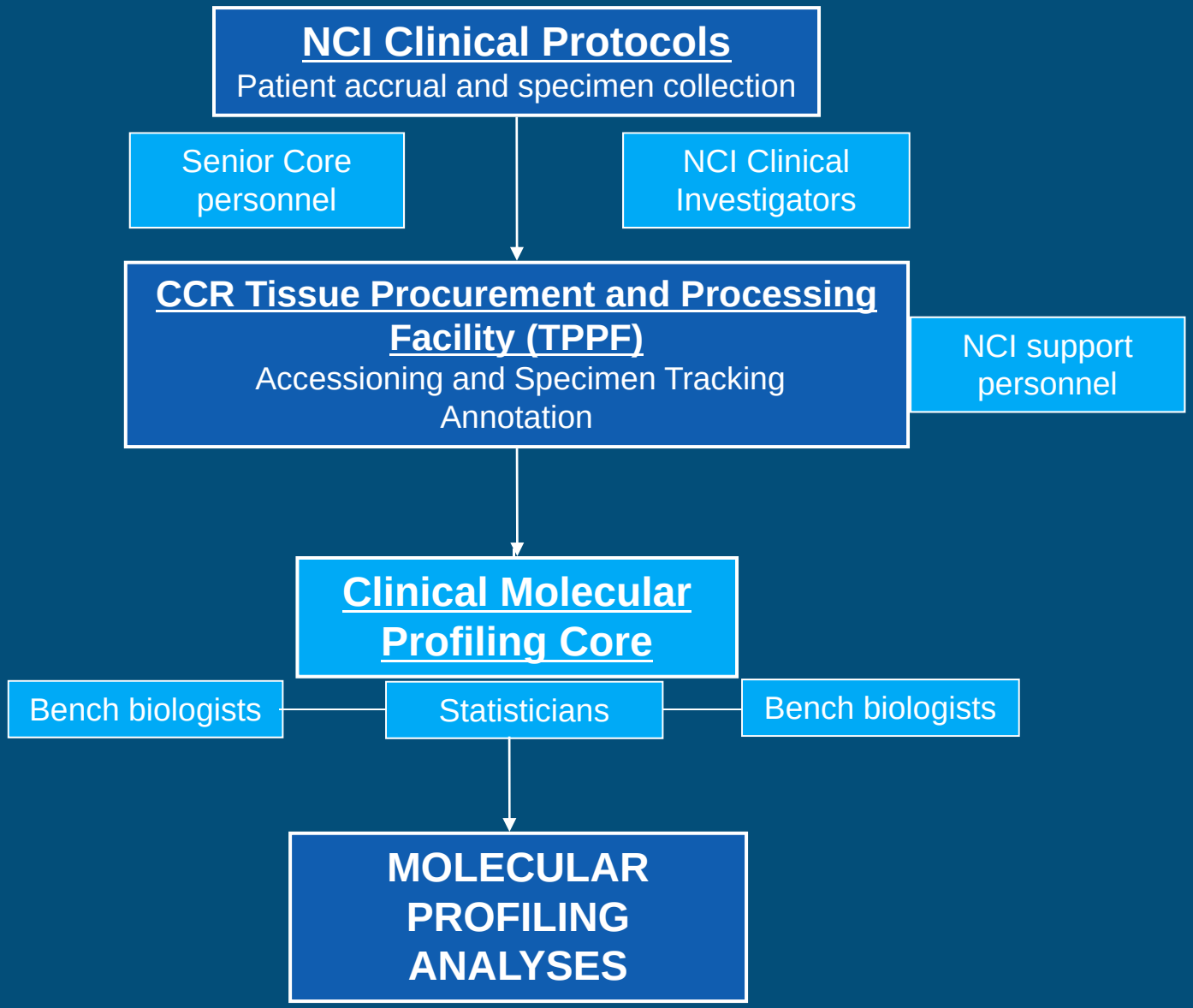
OPPORTUNE BECAUSE OF MATURATION OF TECHNOLOGIES AND GROWING DATABASES OF CANCER GENOME DATA

Clinical Molecular Profiling Core

RESEARCH GOALS SUPPORTED BY CORE TECHNOLOGIES:

- **TUMOR CLASSIFICATION AND CLASS DISCOVERY**
- **DISCOVERY AND VALIDATION OF PREDICTIVE AND PROGNOSTIC MARKERS**
- **CANCER GENE DISCOVERY**
- **PHARMACODYNAMIC MARKER DISCOVERY AND MONITORING**
- **HYPOTHESIS BASED EXPLORATION OF GENES AND PATHWAYS**
- **CLINICAL CORRELATION OF LAB BASED OBSERVATIONS**

Clinical Molecular Profiling Core



Clinical Molecular Profiling Core

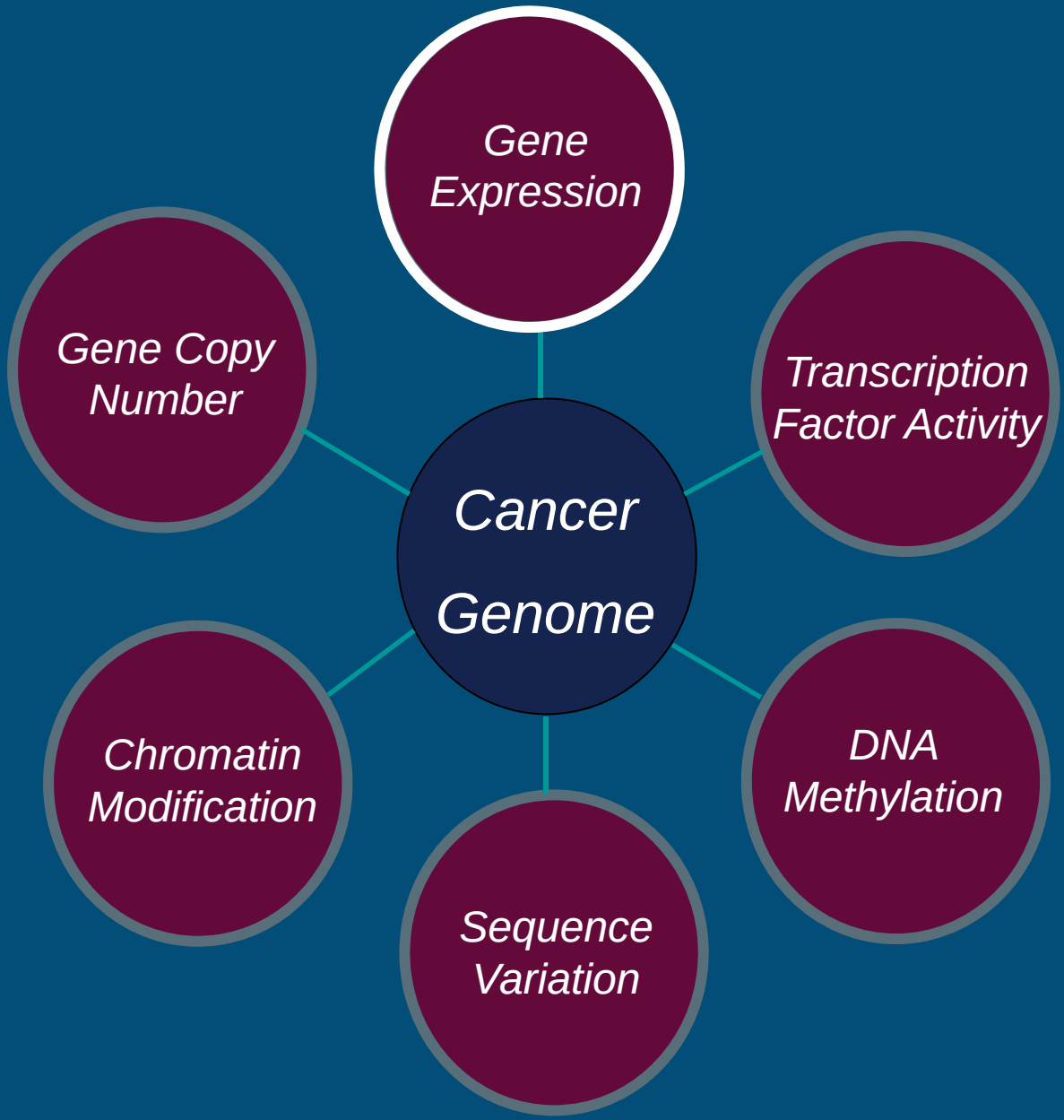
ASSAYS

MICROARRAY AND RELATED TECHNOLOGIES:

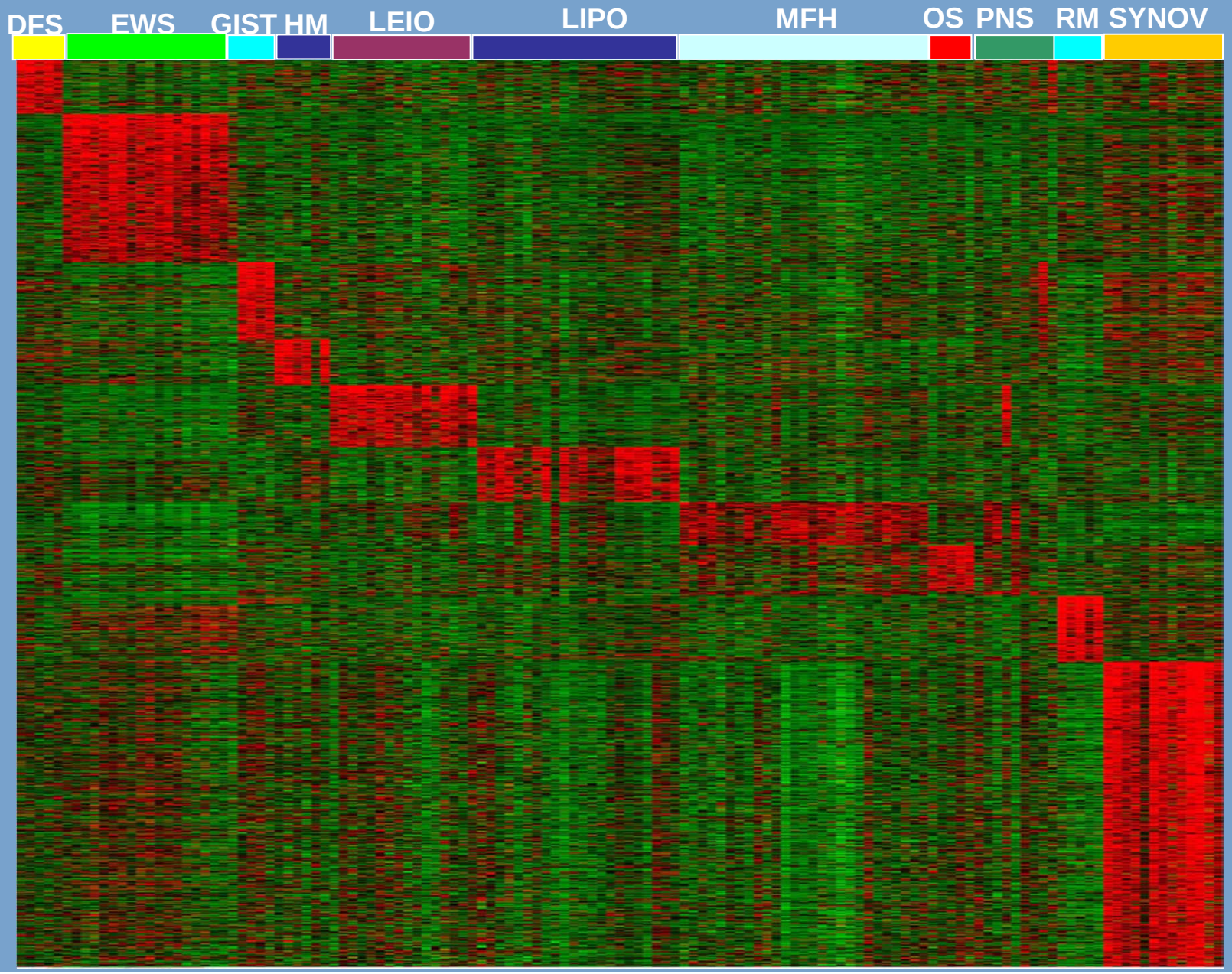
- EXPRESSION PROFILING: CODING GENES AND MICRO-RNAs
- COMPARATIVE GENOMIC HYBRIDIZATION: COPY NUMBER PROFILING
- HIGH DENSITY SNP PROFILING (LOH AND COPY NUMBER)
- CHROMATIN MODIFICATION AND TF LOCALIZATION
- METHYLATION

DNA SEQUENCING

INTEGRATED CANCER GENOMICS

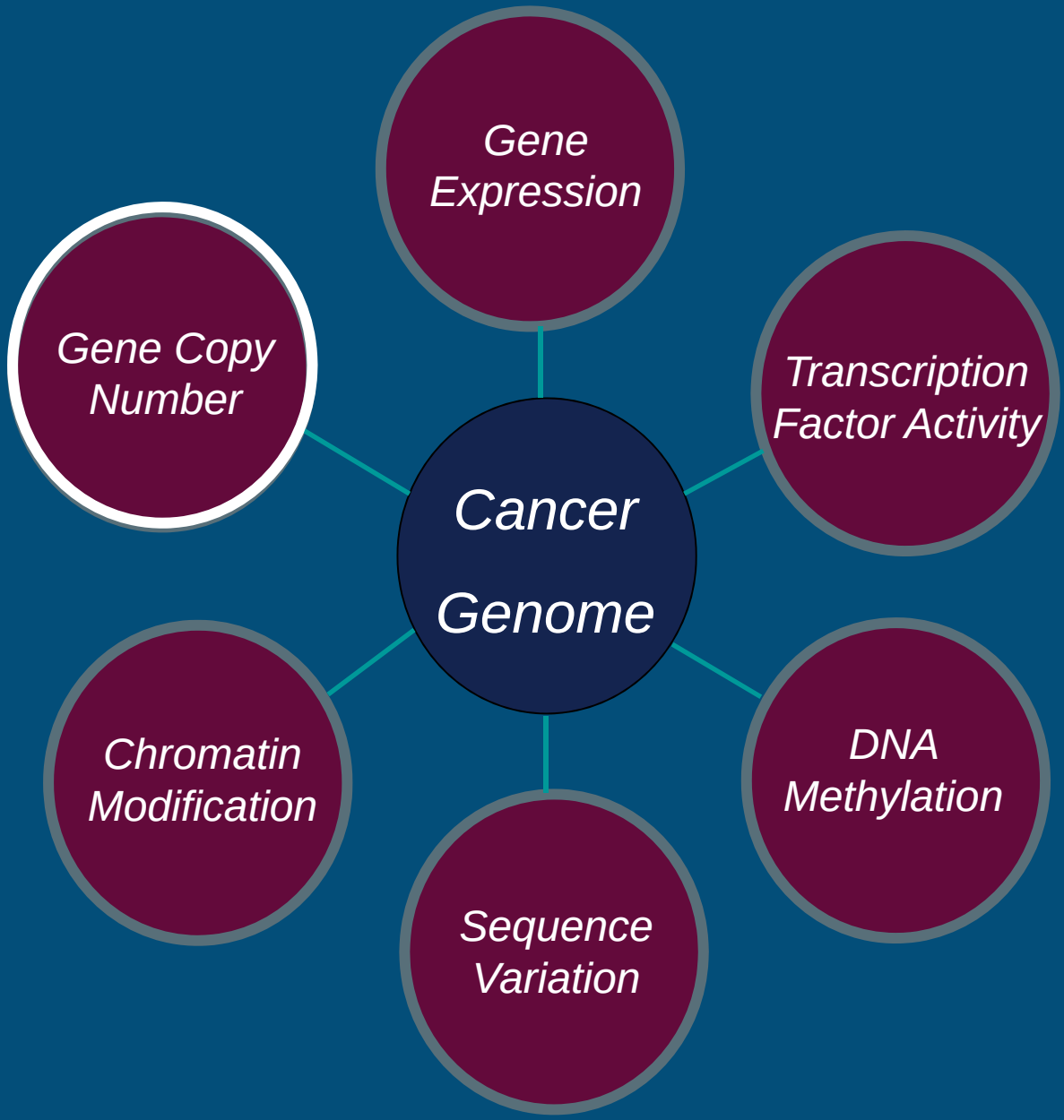


CHARACTERISTIC PATTERNS OF GENE EXPRESSION IN DIFFERENT CANCERS



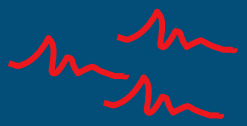
GETTING BEYOND GENE LISTS

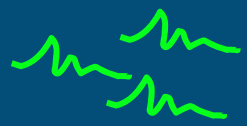
- Optimal use of gene annotations.
- Optimizing use of public data.
- Incorporating data from model systems.
- Linking expression data to sequence.
- Adding other types of genome scale data.


Gene Expression
Gene Copy Number
Transcription Factor Activity
Cancer Genome
Chromatin Modification
DNA Methylation
Sequence Variation

Comparative Genomic Hybridization (CGH) Arrays

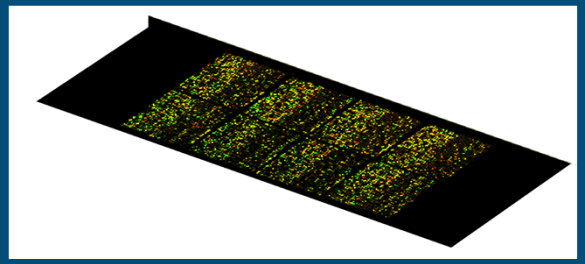
Normal DNA



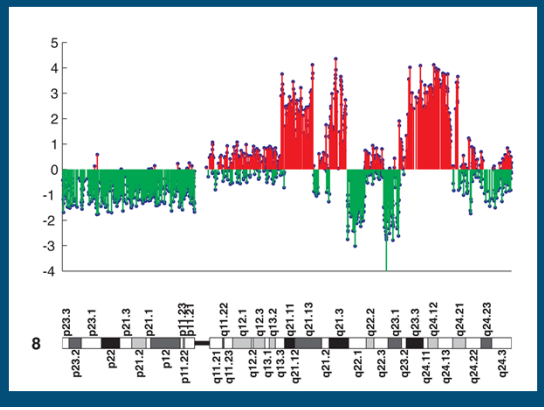


Tumor DNA

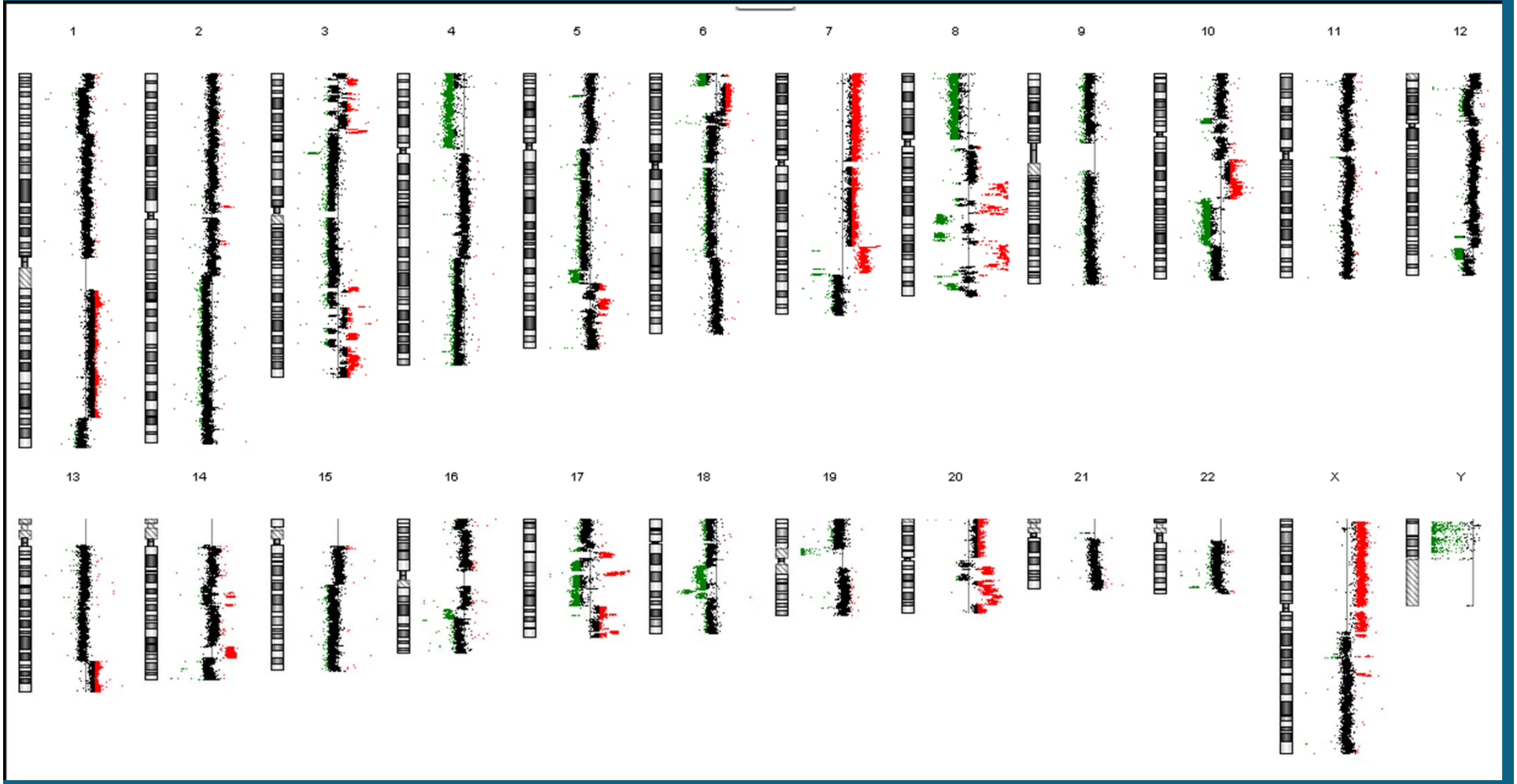
Hybridize equal amounts of DNA to microarray

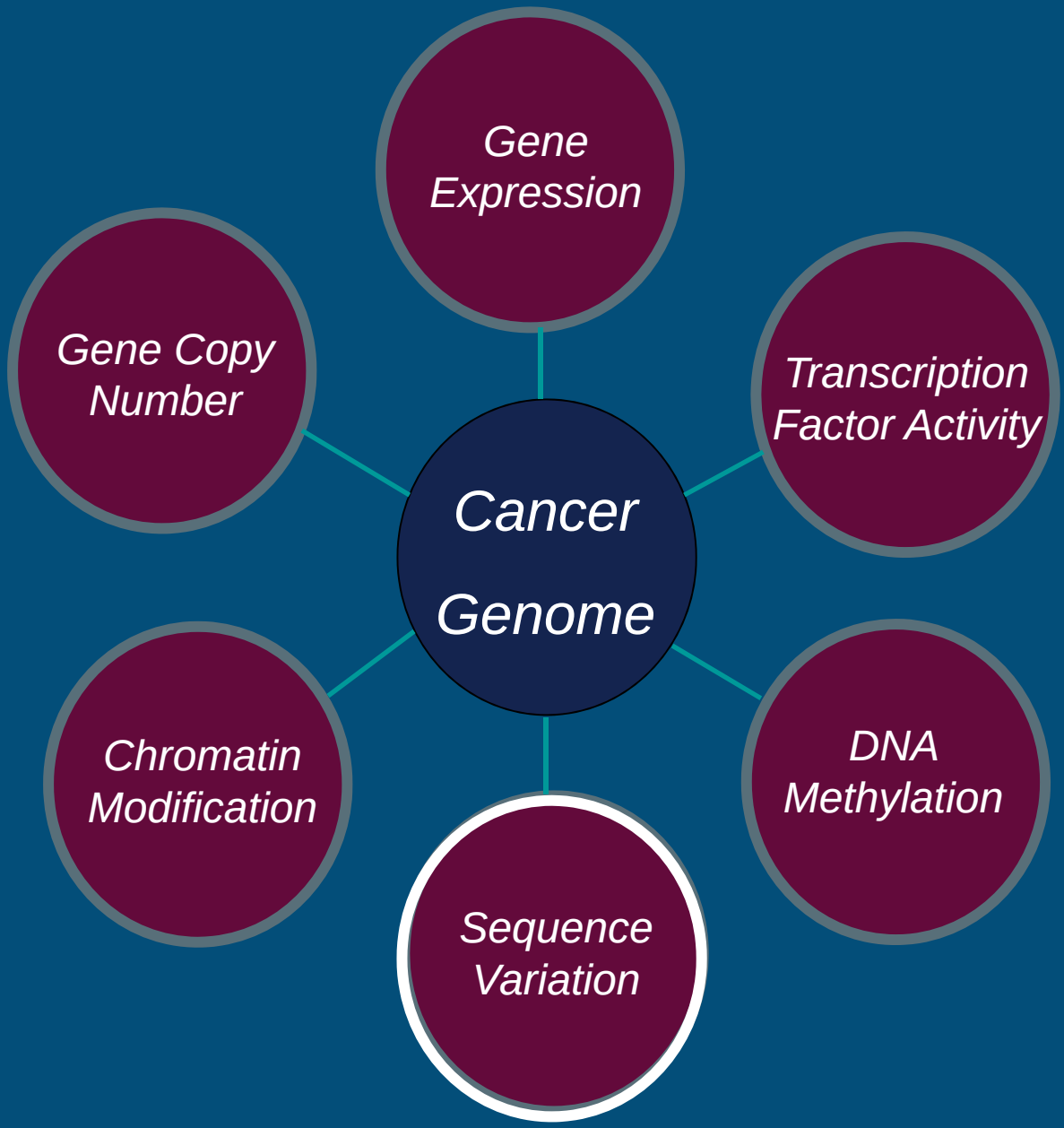


IDENTIFY GENES OF INTEREST IN REGIONS OF CONSISTENT GAIN OR LOSS



ARRAY CGH

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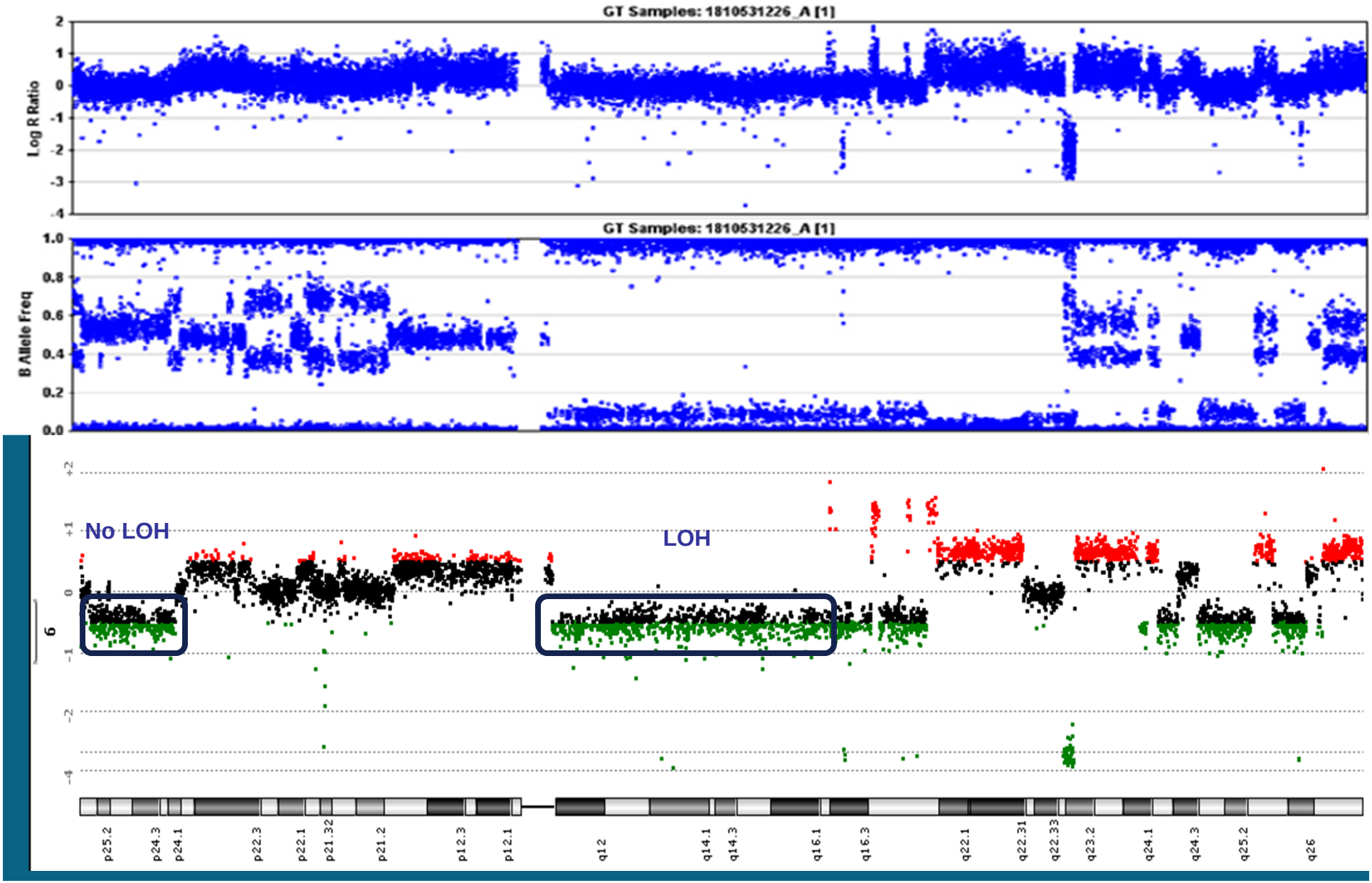
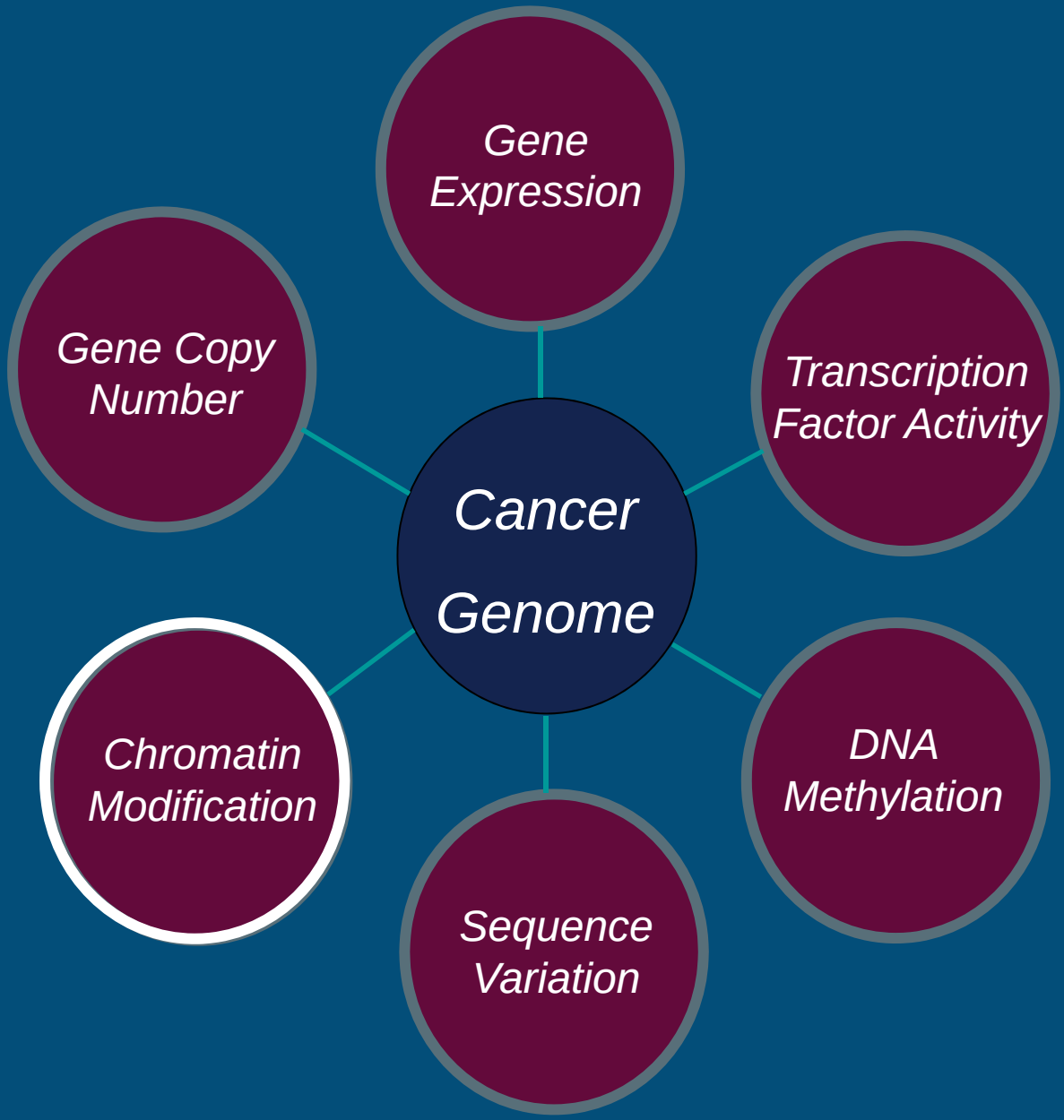
SNP ARRAYS GENERATE ADDITIONAL INFORMATION

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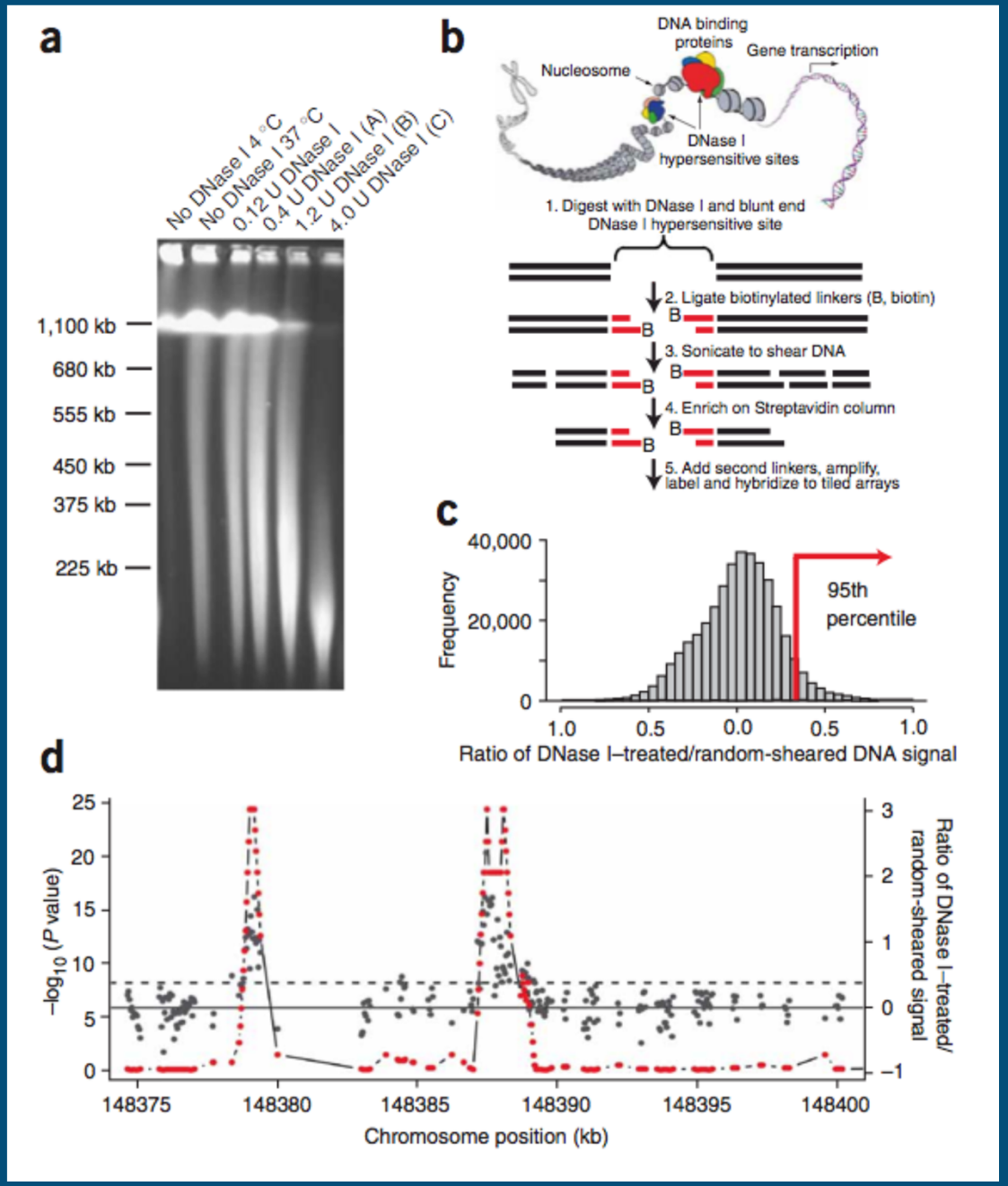
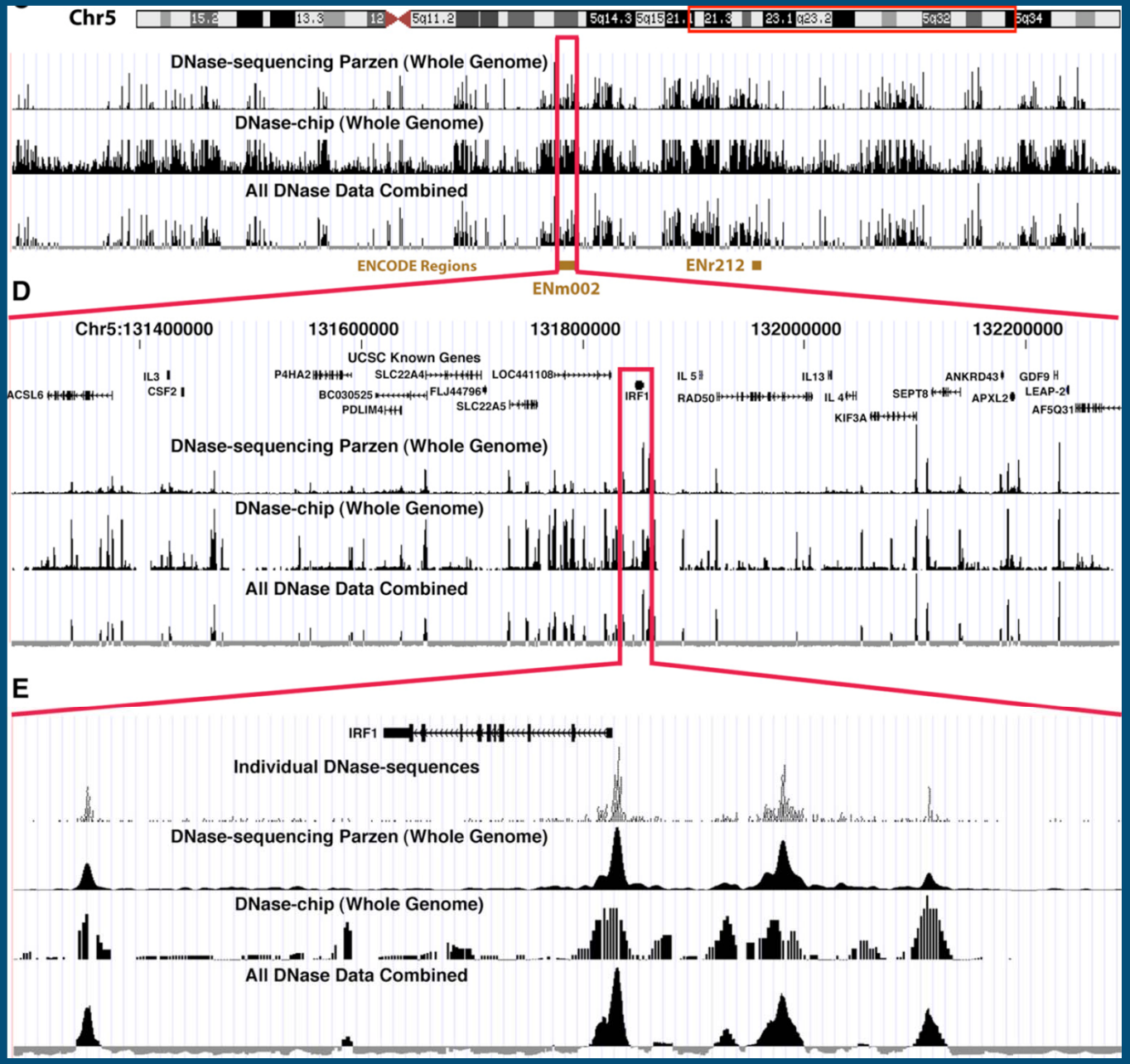
DNase HS Mapping by Microarray

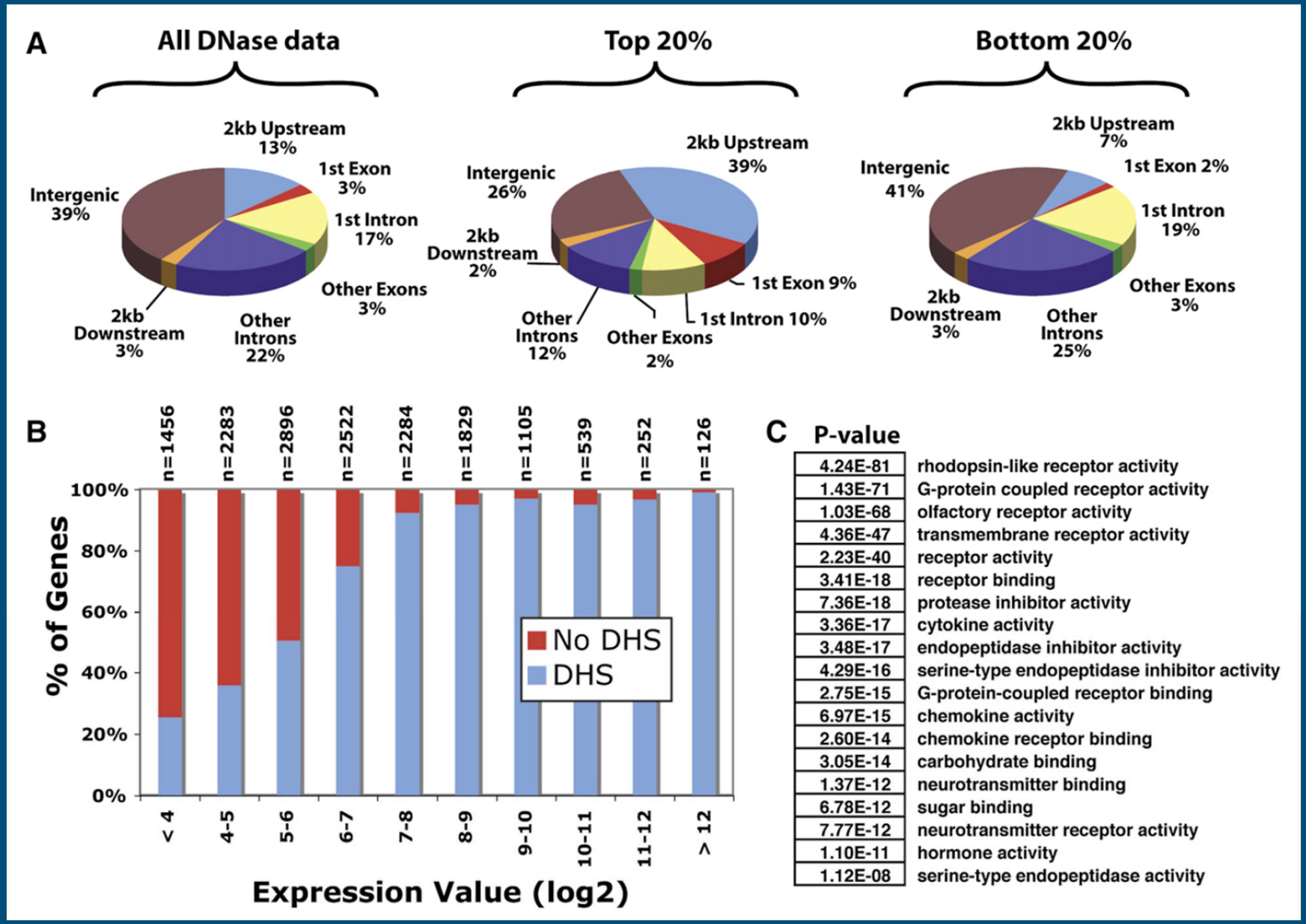


Crawford et al.
Nature Methods 2006

DNase HS Mapping by Microarray and Sequencing



Boyle et al. Cell 2008



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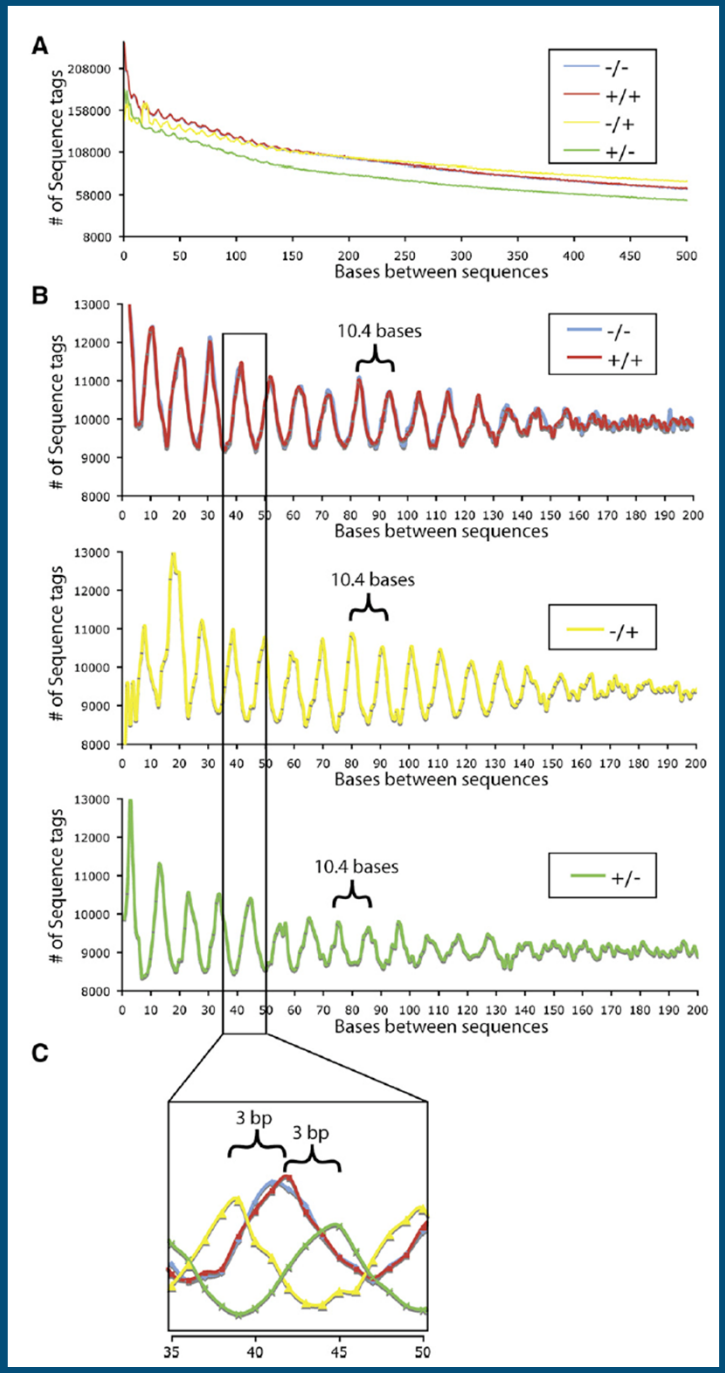
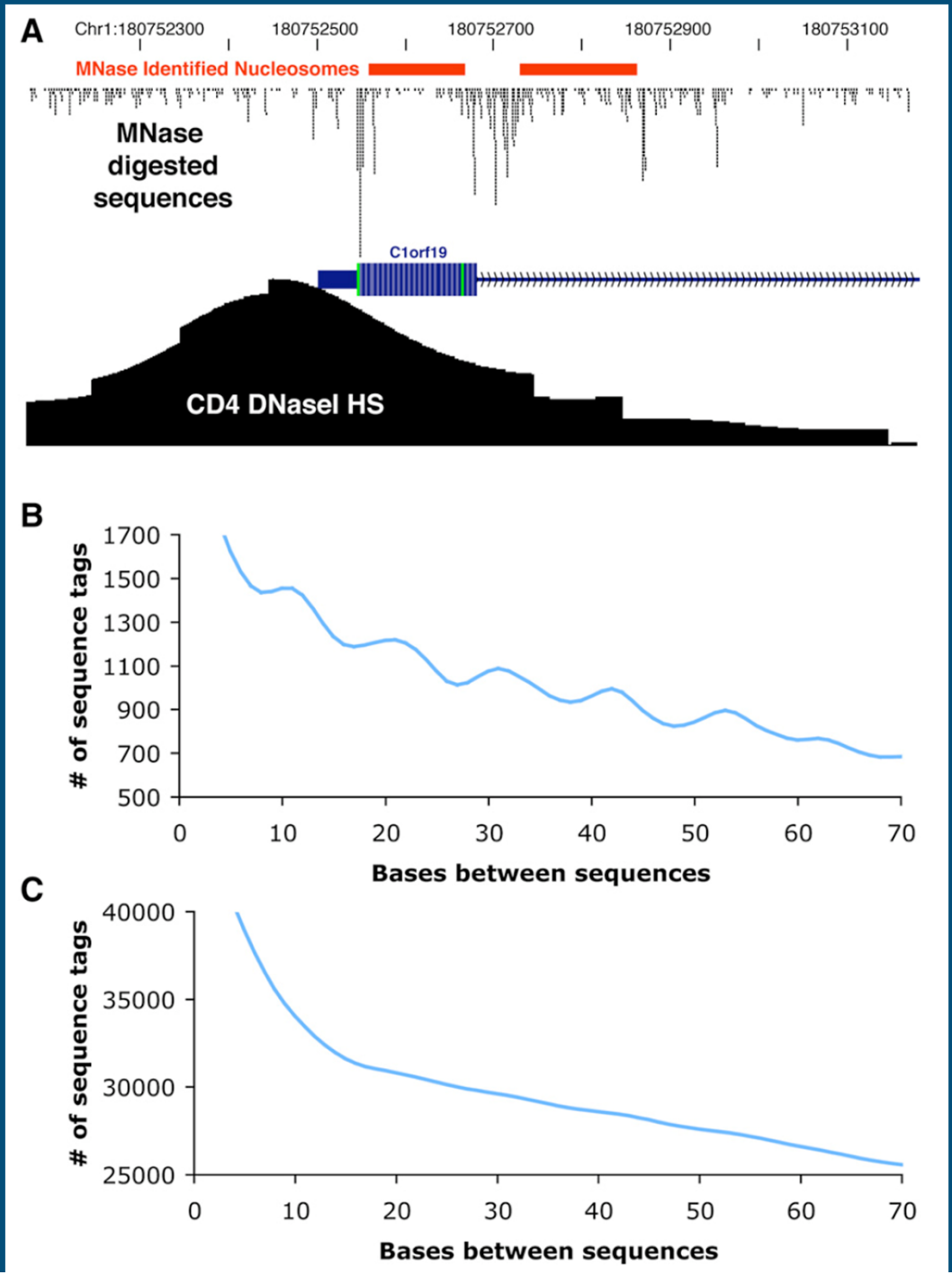


Boyle et al. Cell 2008

Nucleosomes positioned at the boundary of HS sites.



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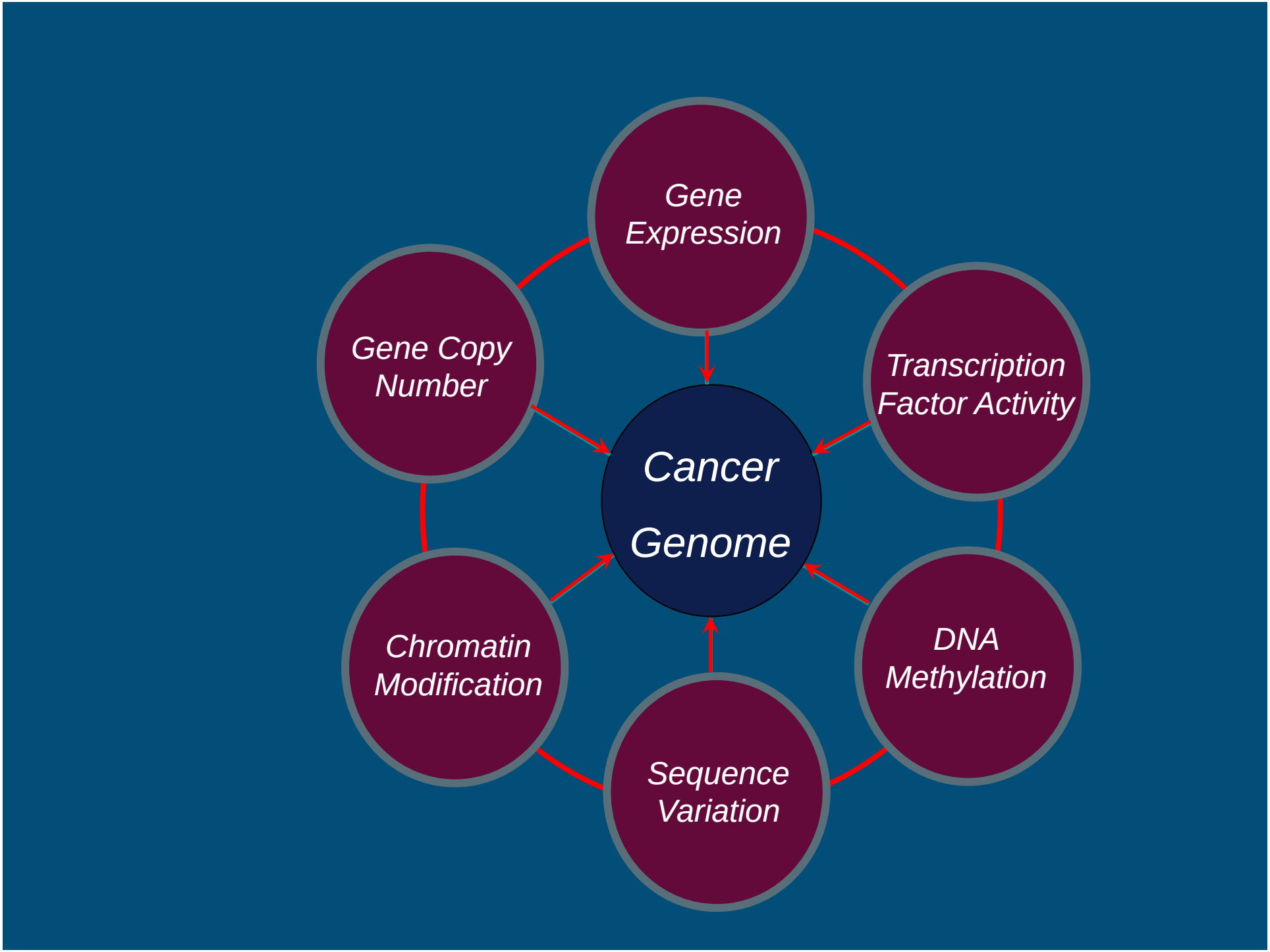
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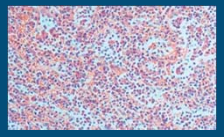
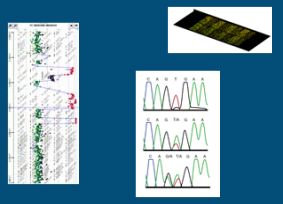
PERSONALIZED CANCER MEDICINE

CONVENTIONAL DIAGNOSIS



MOLECULAR CLASSIFICATION



- Expression profile
- Mutation Scan
- Copy Number Scan

SELECTION OF TARGETED THERAPY

RATIONAL CHOICE OF THERAPIES BASED ON TUMOR BIOLOGY