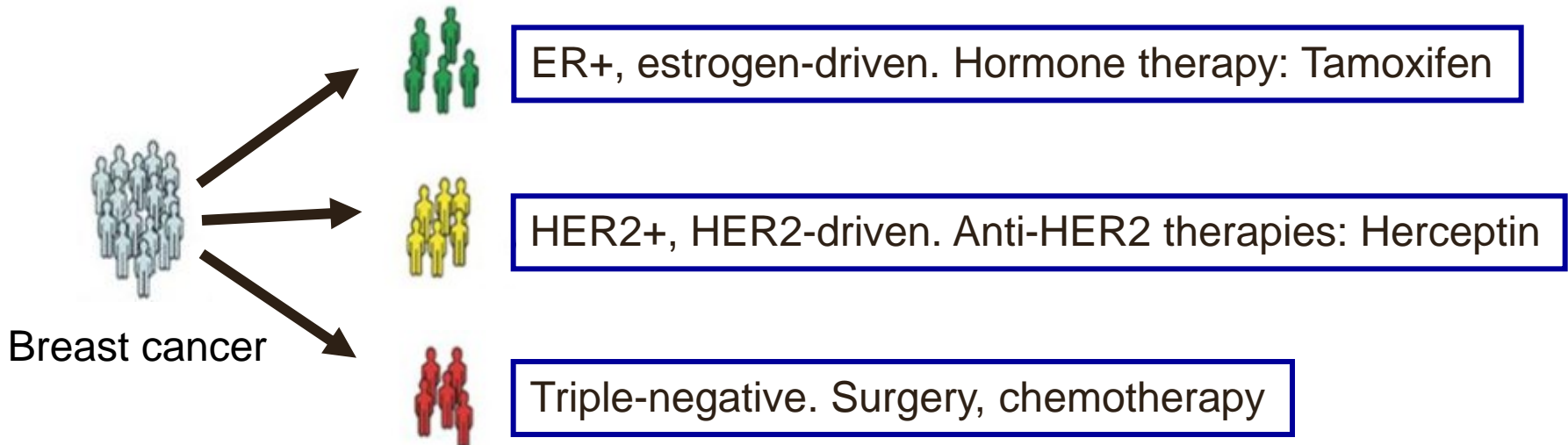


Establishing a human tumor tissue collection for oncology R&D

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Cancer is a heterogeneous disease

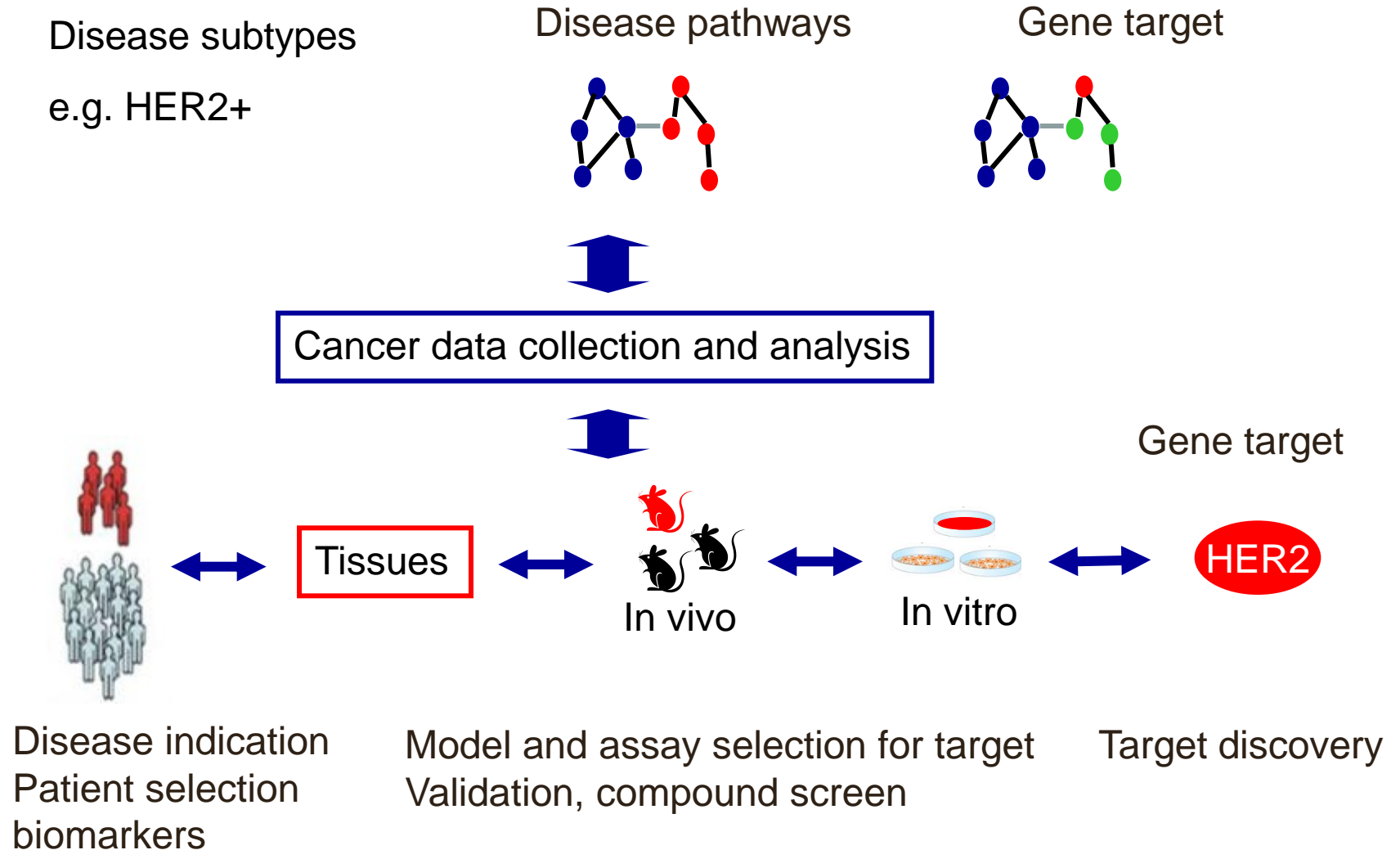
- Cancer is a heterogeneous disease with distinct subtypes:
- Cancer subtypes are different in molecular mechanisms, markers, prognosis, and treatment options



Cancer mechanisms & subtypes can be identified from genomic data

- **Cancer subtypes are traditional defined by tissue origins and histopathology**
- **Molecular and genomic based subtypes: Her2+, ER+, basal, ...**
- **Common genomic alterations in cancer**
 - **Oncogene activating mutation: KRAS, EGFR**
 - **Oncogene copy-number amplification: > 10 copies of HER2 in some breast cancers**
 - **Over-expression of oncogene**
 - **Deletion of tumor suppressor genes: TP53, PTEN, ...**
 - **In-activating mutation in tumor suppressor genes**
 - **Down-regulation of tumor suppressor gene expression**
- **Cancer genomic data can be obtained by sequencing (mutation), mRNA chip (expression), and SNP chip (copy-number, LOH)**

Cancer tissue and genomic data is essential for oncology R&D



Why do we need an in-house tumor tissue collection?

Limitation of past BMS tumor tissue collections

- Restriction on clinical trial samples
- Limited sample/data purchases over time, quality and quantity varies

Limitation of public cancer data

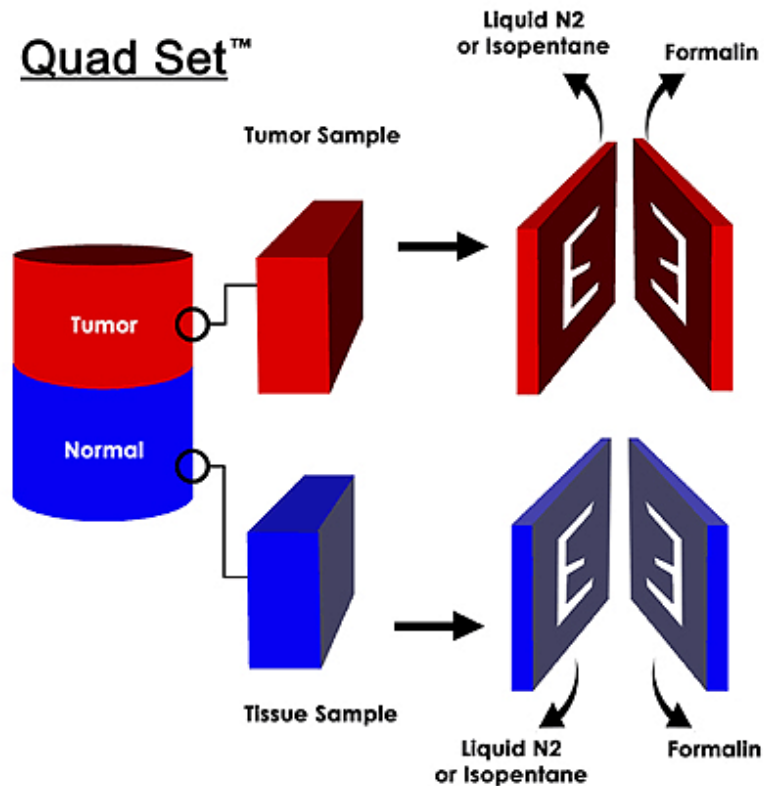
- Published data are not complete
- Different technologies makes it difficult to compare datasets.
- Original material not accessible for additional analysis (e.g., p53 status, kinase mutations, and HER2 status)

Requirements for BMS tumor tissue collection

Requirements:

- **Cover specific tumor types with sufficient sample sets and variations**
- **Tumor and matched normal tissue from the same patient**
- **Complementary FFPE tissue sets for IHC**
- **Associated history of patient information**
- **Sufficient material to allow initial cancer genomic data generation and later experiments**
- **Comprehensive cancer genomics data collection**
- **Establishment of central repository of data and material**
- **Bioinformatics for data storage and analysis, sample search and retrieval**

Quad Sets of samples from Asterand



Major tumor types of interests:
breast, colon, lung, ...

Enough samples to cover
tumor variations

Comprehensive annotation is important for sample usefulness

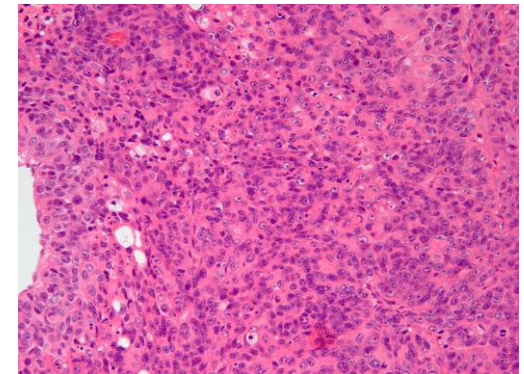
Patient Information

- Basic patient information (age, sex, BMI,...)
- Smoking status and amount
- Alcohol use

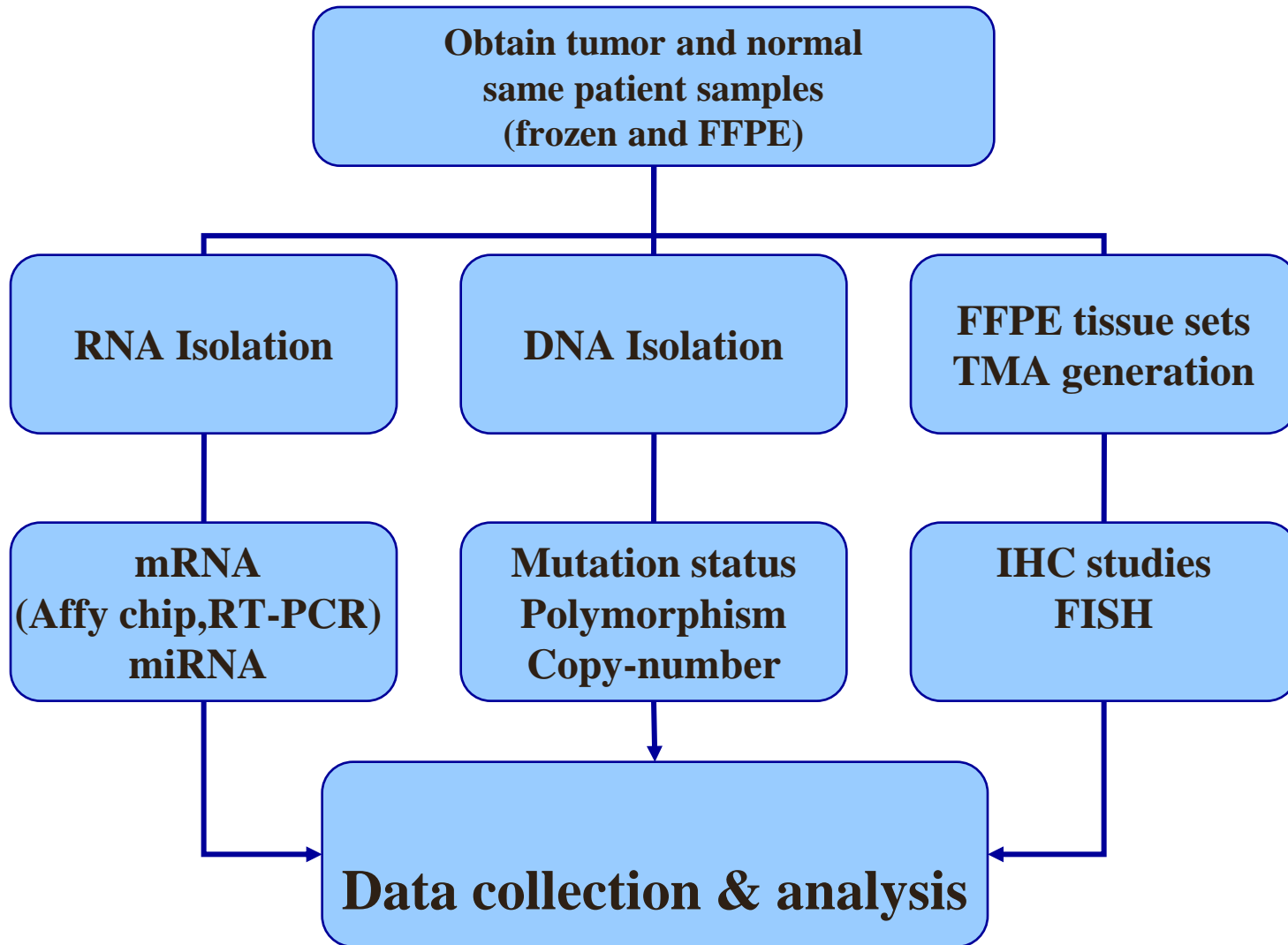
Tumor information

- Biosample confirmed diagnosis
- Grade, stage,...
- Percent tumor vs normal vs necrotic
- Percent tumor cells vs normal vs stromal vs inflammatory
- Molecular markers (HER2, ER/PR status)

HE images



Plan for reagent and data generation

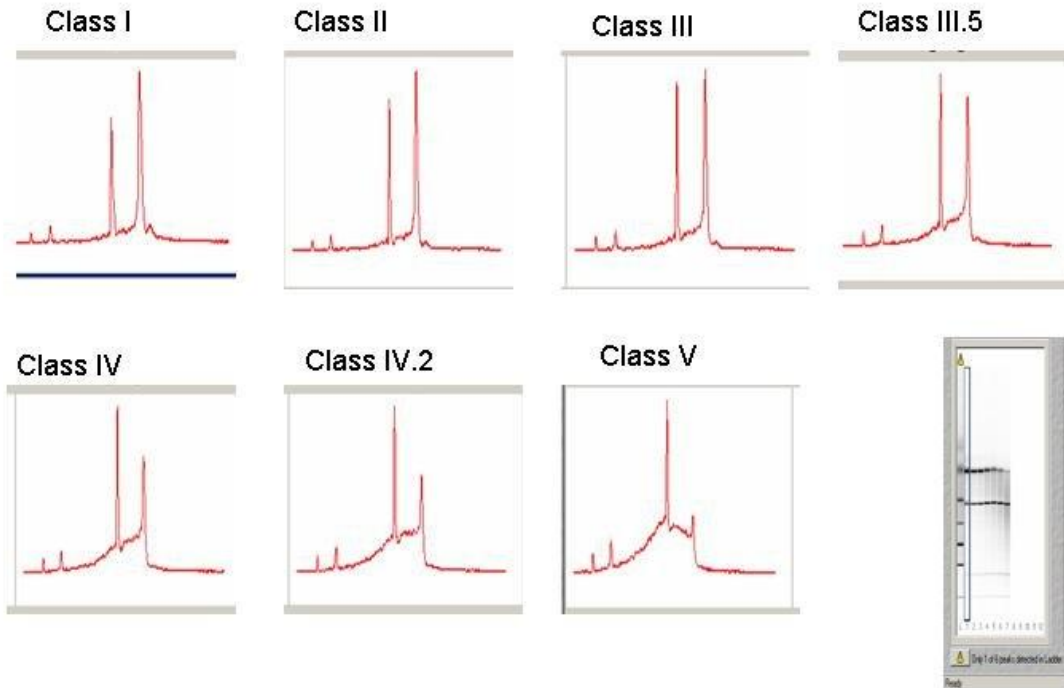


Rigorous quality control in reagent and data generation

RNA samples analyzed with Agilent Bioanalyzer

DNA samples on gel

RNA Classification:



Genomic characterization

Genomic data analysis plan

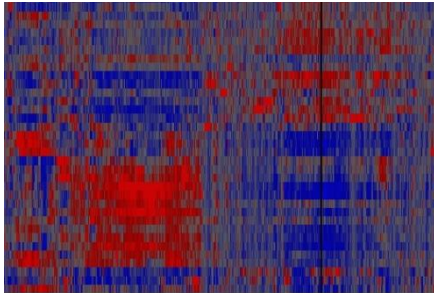
Basic characterization of tumor samples, check for:

- Consistent with literatures
- Similar to “typical” tumors
- Coverage of tumor variations

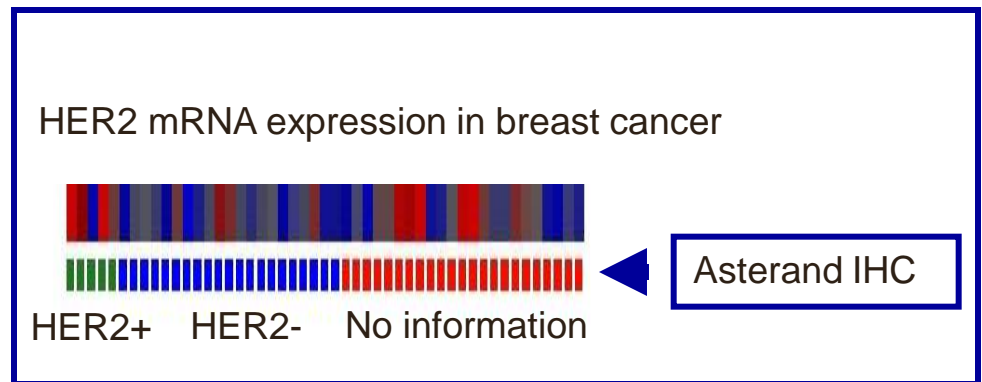
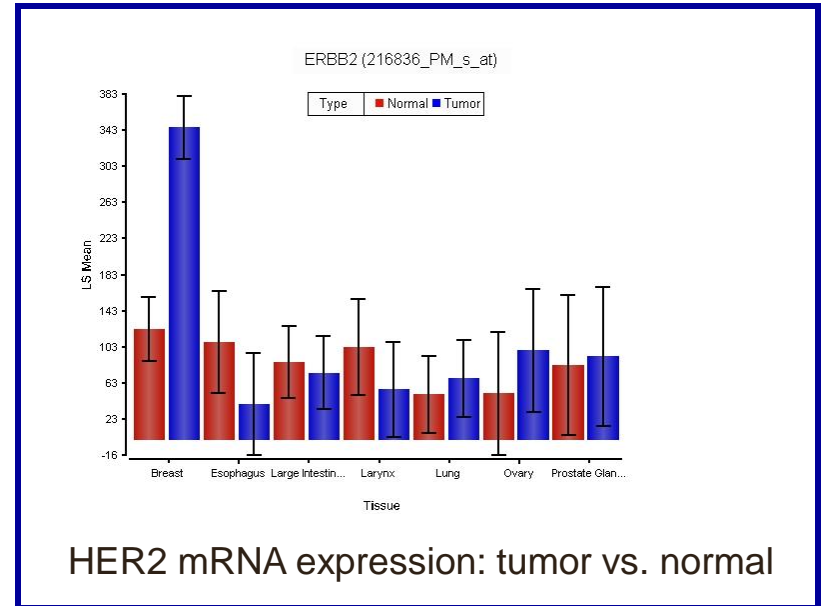
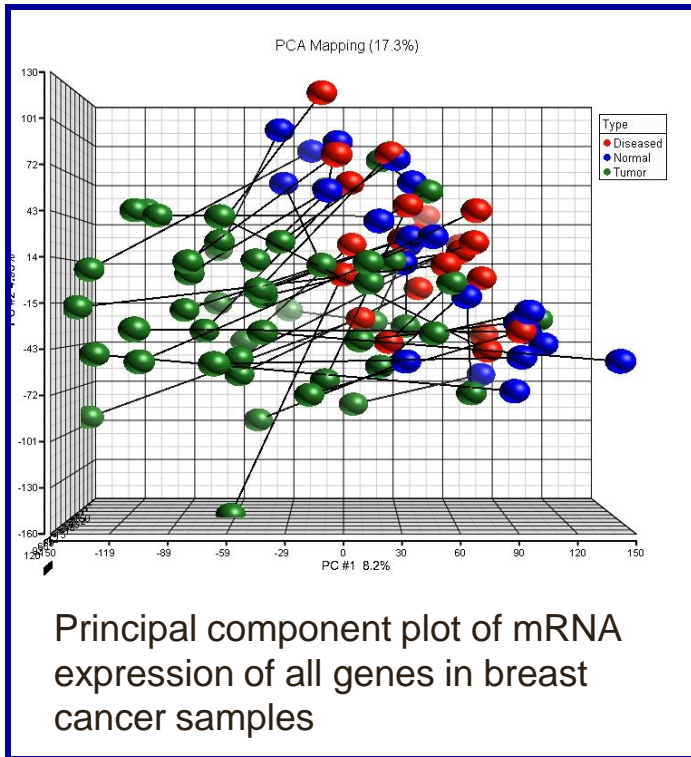
Deep data analysis

- Target discovery (e.g., genes with tumor over-expression)
- Provide base-line cancer genomic information for BMS targets and biomarkers
 - Tumor vs. normal expression in specific tumor subtypes or in all tumors
 - Copy-number gain or loss in specific tumor subtypes or in all tumors
 - Association with known subtypes
- Generate genomic signatures for clinical annotation, pathways status, or gene mutation; compare with public data when possible
- Integrate expression, copy-number, and mutation information
- Gain insights in cancer disease biology

Genomic characterization of BMS tumor samples

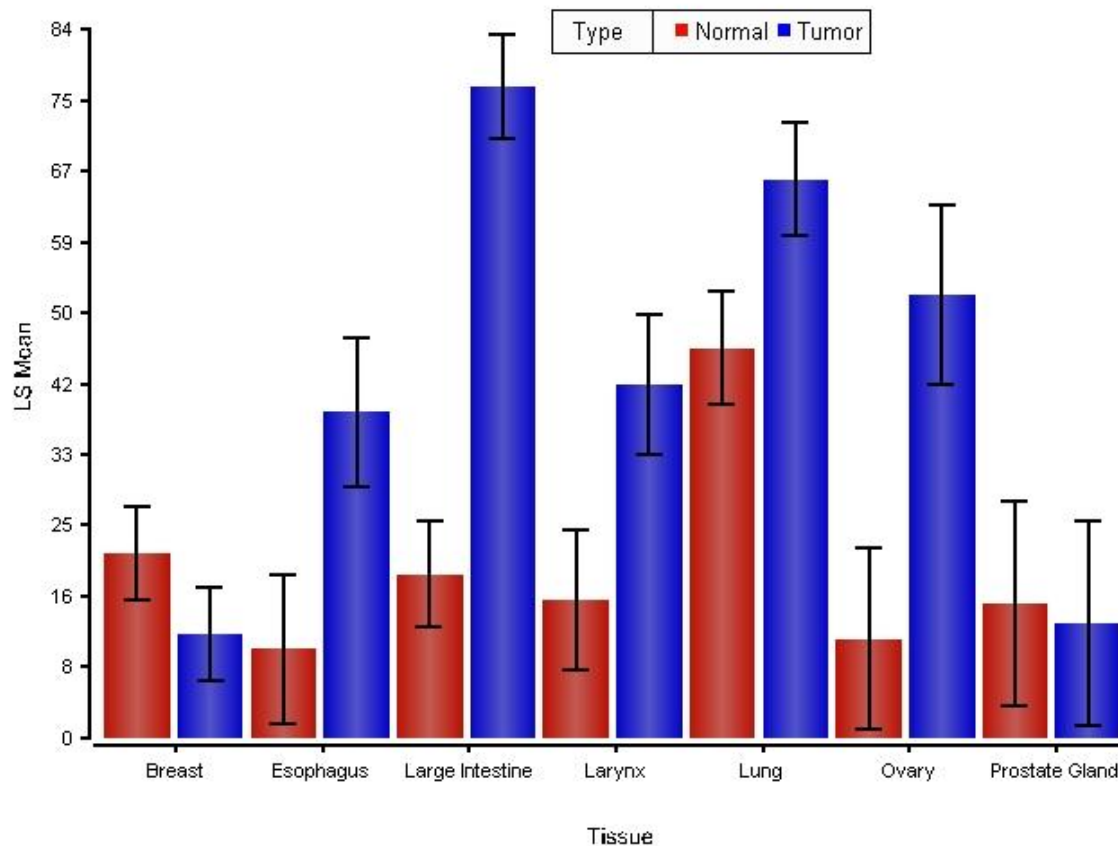


clustering



Base-line expression data for a BMS target gene helps model selection and disease indication

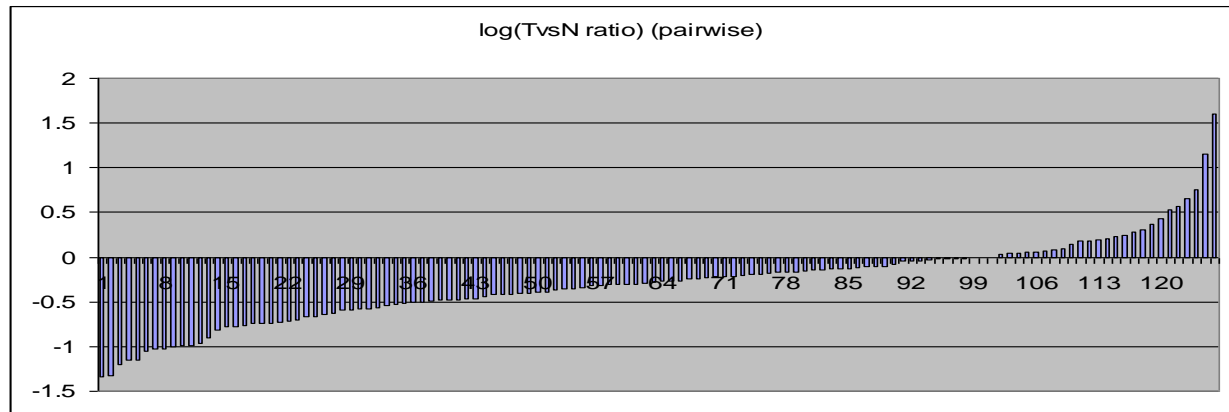
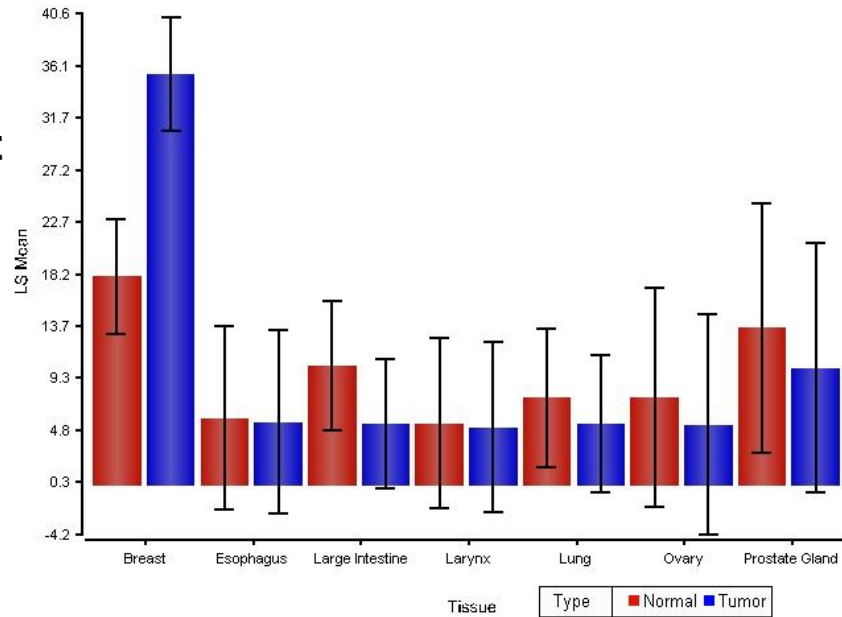
Essential information for disease indication and assay/model selection



Base-line expression data for another gene

Similar to HER2

- Over-expressed only in breast cancer
- Only in a subset of breast cancer patient (not overlapping with HER2)



Breast cancer vs.
normal expression
in individual patient

Generate genomic signature of clinical status: ER status as an example

- Genes over-expressed in ER+ vs. ER- samples in BMS breast tumor samples. Significant overlapping with published ER signature in breast cancer

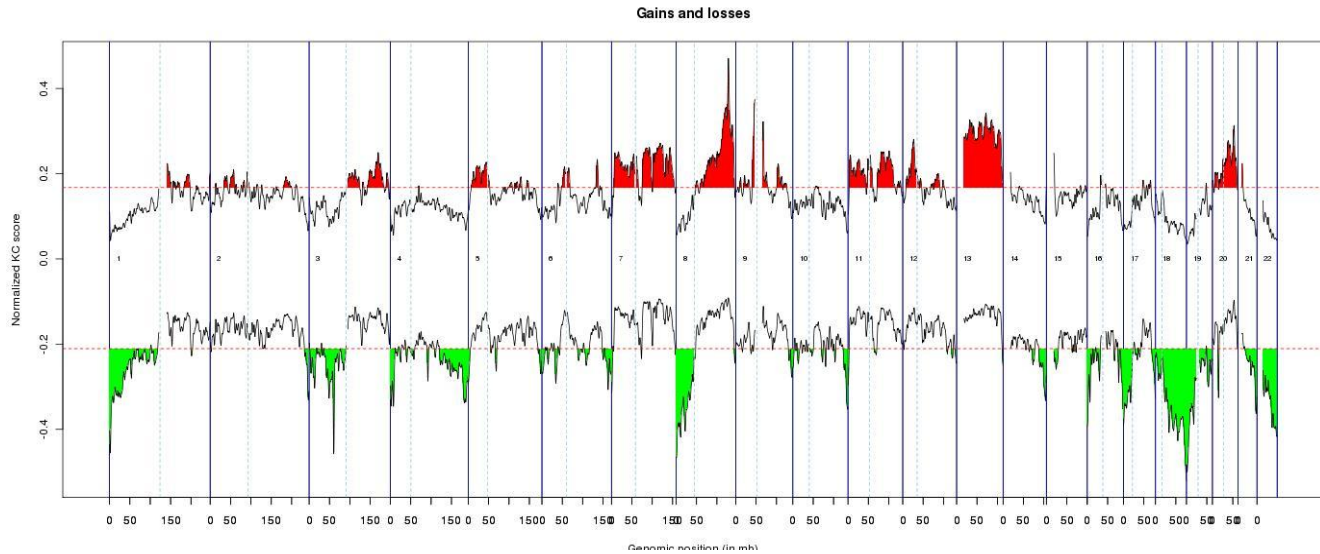
Description	<u>LOD</u>	<u>Odds</u>	<u>Odds-Corr.</u>
Genes whose expression is consistently positively correlated with estrogen receptor status in breast cancer - higher expression is associated with ER-positive tumors	15.6	2.31e-16	4.21e-13

Cancer cell-line collection at BMS

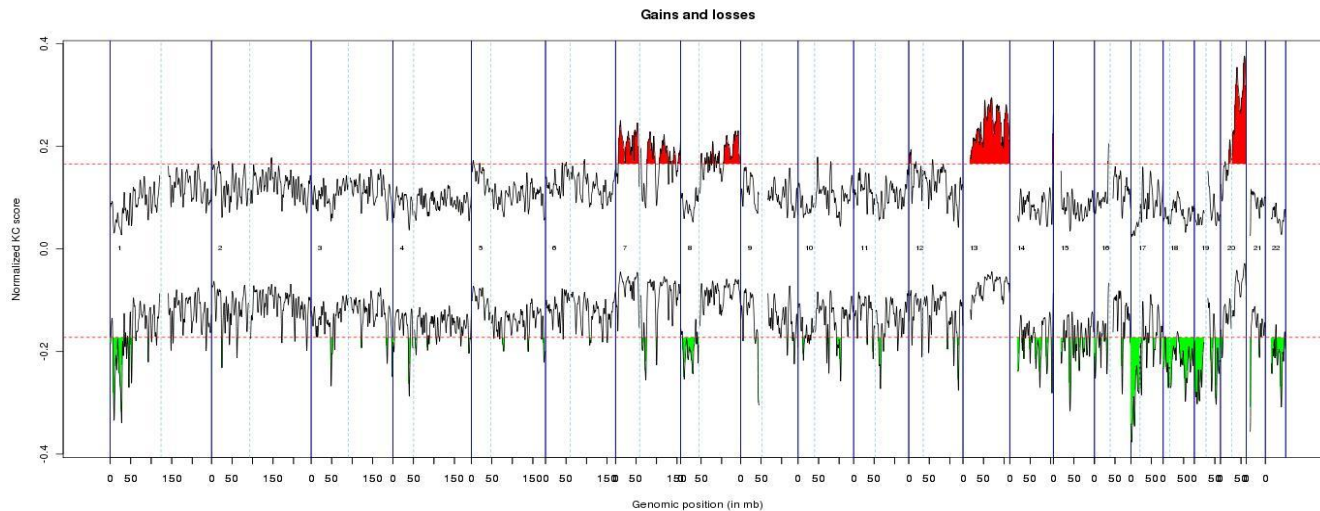
- **Cell-lines are essential research tools**
 - **Target validation**
 - **Compound screen**
 - **Biomarker discovery**
 - **Mechanisms of action**
- **Genomic datasets (expression, genotypes, mutation, copy-number, LOH) generated for several hundreds cancer cell-lines**
- **Keys question: how similar are cancer cell-lines compared with primary tumors**
- **Compare genomic data of cell-lines with primary tumors could provide clues**

Compare cell-line collection with primary tumors: similar copy-number profiles

Copy-number
profile in cell-
lines



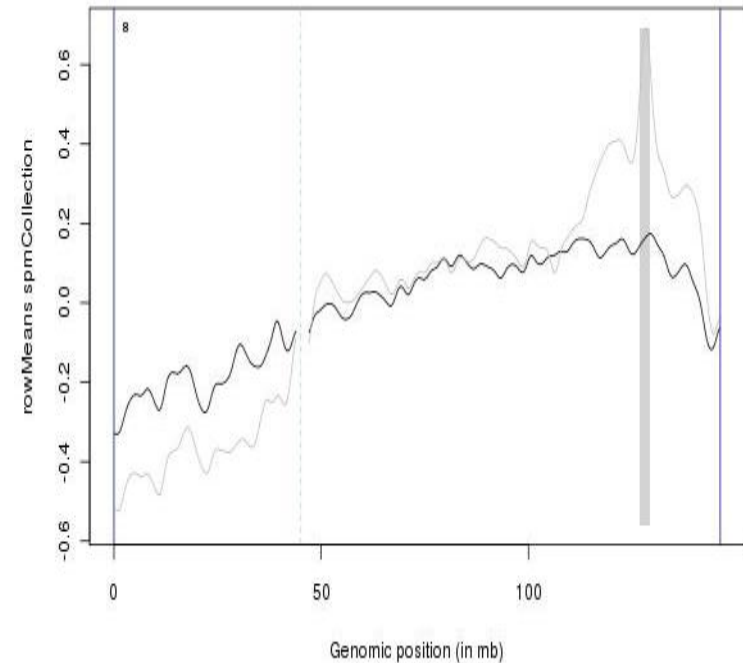
Copy-number
profile in
tumors



Use tumor collection to test hypothesis

- Certain copy-number changes are associated with mutation of an oncogene in cell-lines
- Regions may contain genes involved in cancer biology related to the oncogene
- Plan to sequenced the oncogene in BMS tumor collection, test association with copy-number changes

Copy-number changes associated with mutation of an oncogene in cell-lines



Summary

- **We are establishing an in-house collection of human tumor tissues and associated genomic datasets.**
 - **Quad sets of samples of major tumor types**
 - **Rigorous quality controls**
 - **Thorough genomic characterization**
- **Growing impacts on BMS oncology R&D**
 - **Target discovery and validation**
 - **Biomarkers discovery and validation**
 - **Cancer disease biology**

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