

UCSF Helen Diller Family
Comprehensive
Cancer Center

Research Infrastructure to Support

Personalized Medicine

Translational Informatics

Sorena Nadaf, M.S. M.MI

*Director - Translational Informatics,
CIO*

Bio-IT World

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A Fact:

- “Science is evolving at an incredible pace. It’s a revolutionary period. The fundamental change is that biomedical science has converged...
 - Elias Zerhouni, M.D.

A Complicated Question:

A clinician would like to perform a study to compare the types of cancer treated with a particular chemotherapeutic agent, involved in clinical trials, in which the study subjects lived longer than 2 years post-study to find gene expression patterns that might be predictive of a positive outcome. The researcher has expression (Affy), and Mass Spec data for patients that lived less than two years, and is interested in performing “Shotgun” Proteomic Analysis on the same subset of patient samples, and provide his colleagues in Japan blinded data sets for quantification and quality control experiments.

A Complicated Query:

- Same Investigator needs to collect all available NGS data, from lung cancer patients that were part of specific clinical trial protocols using Taxol within the past five years. In addition, the investigator needs data from available tissue samples, localized within 10mm of tumor site from this patient population such that she can perform further studies. Finally, her need to identify all severe adverse events for the identified patients that had a severity rating of 4 and are likely linked to Taxol administration.

Description of Challenges:

- The landscape of clinical, basic science, and translational research is **changing**
- **Enabled by:**
 - High Throughput Molecular Science
 - Ubiquitous data communications & computing
- **Driven by national programs:**
 - NIH / NCI Roadmaps
 - Translational & Biomarker Discovery Programs like SPORE' s and SPECS
 - CTSA' s

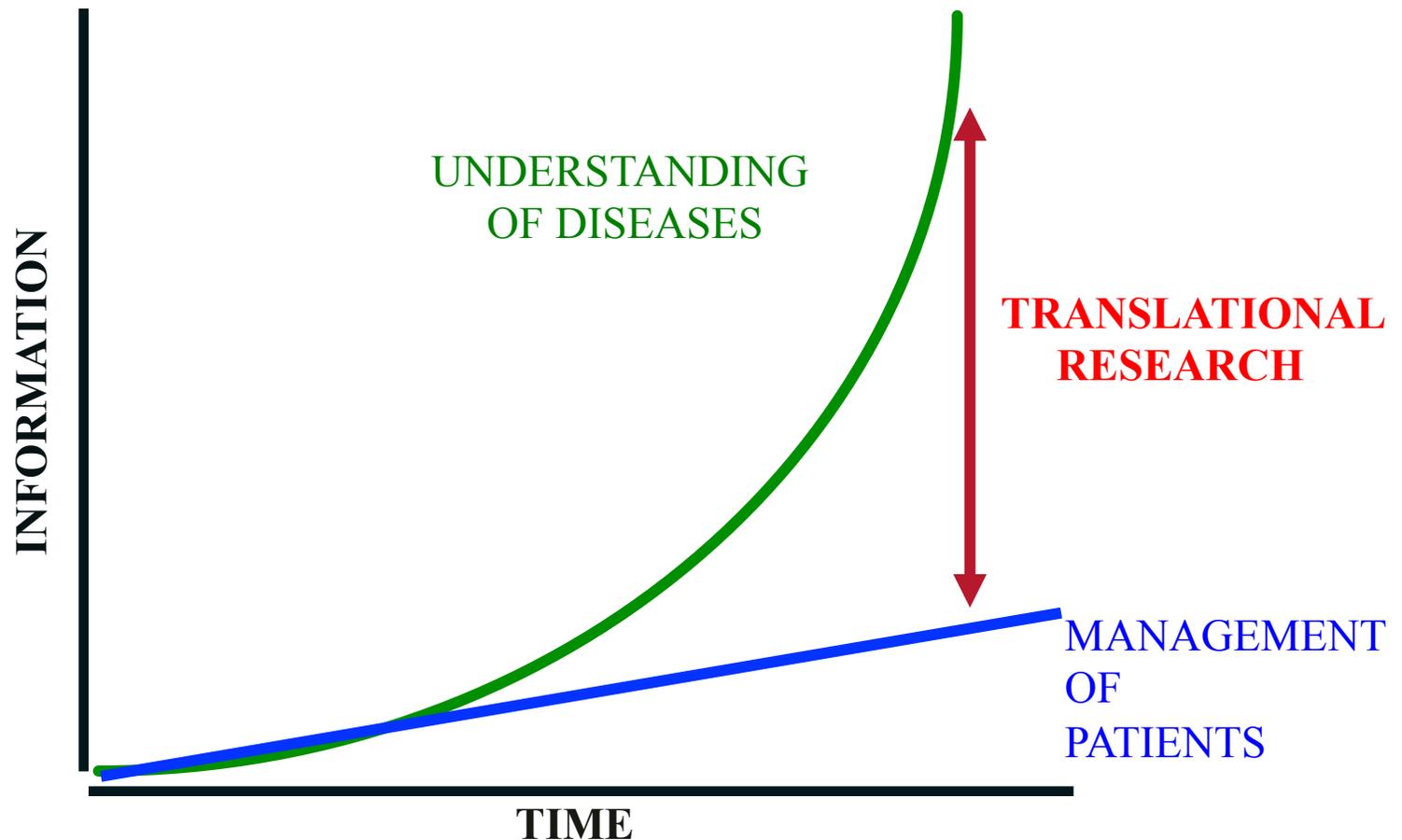
What will it take?

- “Translating” Translational Research into Practice:
 - ① Why?
 - ② How?
 - ③ With What ?

21st Century Translational Research

Accelerating Personalization of Care

Challenge: Filling in the Gap



Goals of Translational Research

- Bridge the lab and clinic in both directions
- Accelerate development of individual targeted agents
 - ✓ Small molecules
 - ✓ Antibodies
 - ✓ siRNAs
- Accelerate development of individual biomarkers
 - ✓ Risk
 - ✓ Tumor Burden
 - ✓ Predictive markers for response
- Link molecular diagnostics and therapeutics to *personalize patient care*

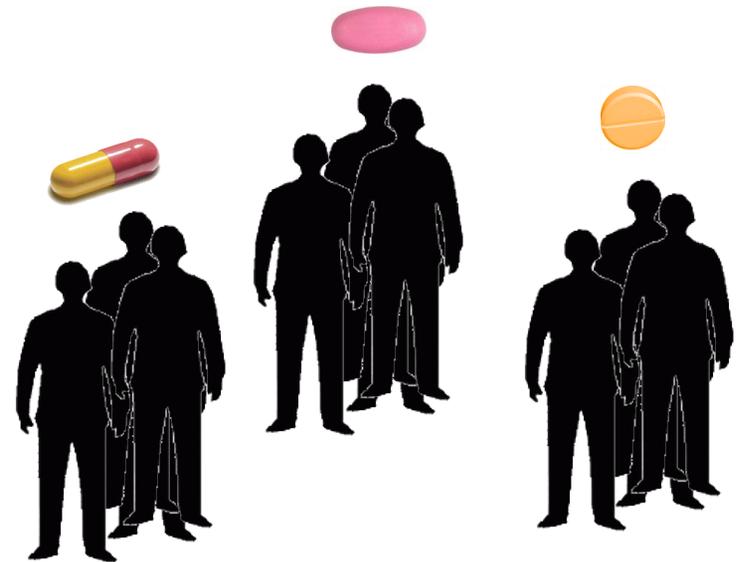
What is Personalized Medicine?

Current Practice



Trial and Error
Trial and error

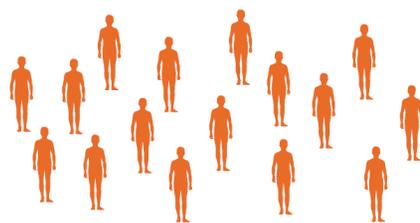
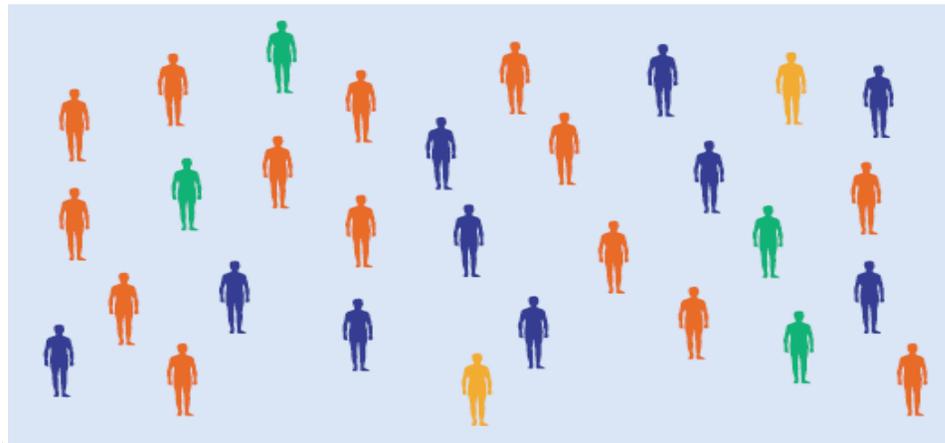
Personalized Medicine



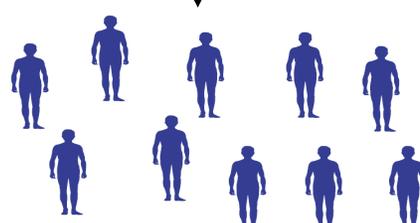
The **right treatment** for
the **right person** at the
right time

Personalized Medicine

PATIENTS WITH SAME DIAGNOSIS ARE NOT ALL THE SAME



**Predicted good response
to drug or combination
of drugs**



**Predicted poor or no
response to drug or
combination of drugs**



**Increased Likelihood of
toxicity of drug or
combination of drugs**

CHANGE DRUGS

CHANGE DRUGS

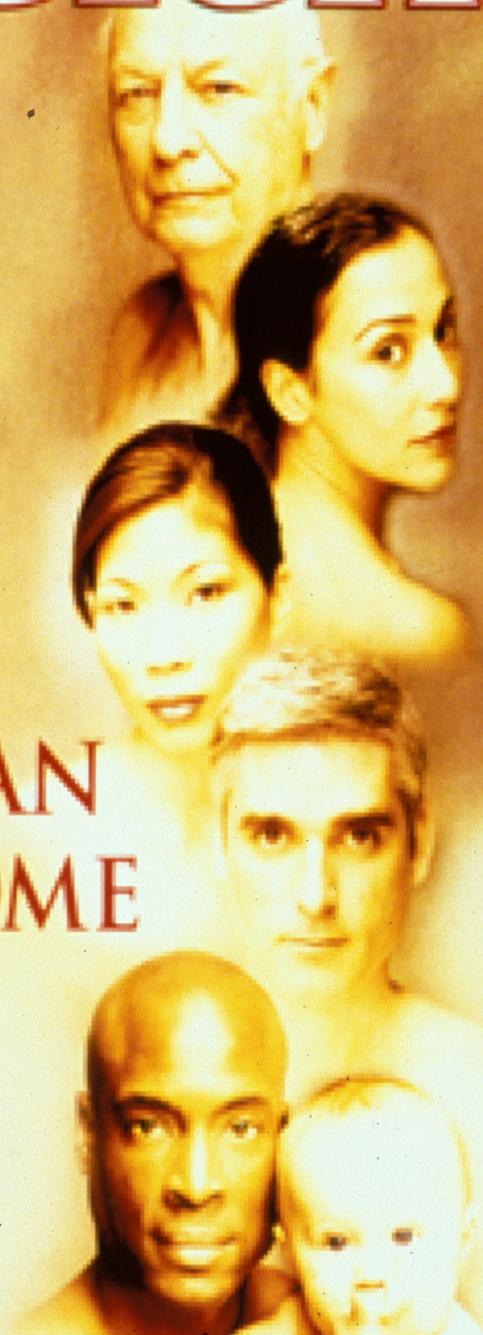
Coping with the Heterogeneity of Cancer

- Cancers develop at 100' s of Different Sites
- Most are Clonal and arise from the Progeny of a Single Cell that accumulate at Least 5 Mutations
- With >100 Oncogenes and Tumor Suppressor Genes, >10 Billion Different Combinations are Possible
- Given Genetic Differences Between Patients with Cancer, no two Cancer are Exactly Alike

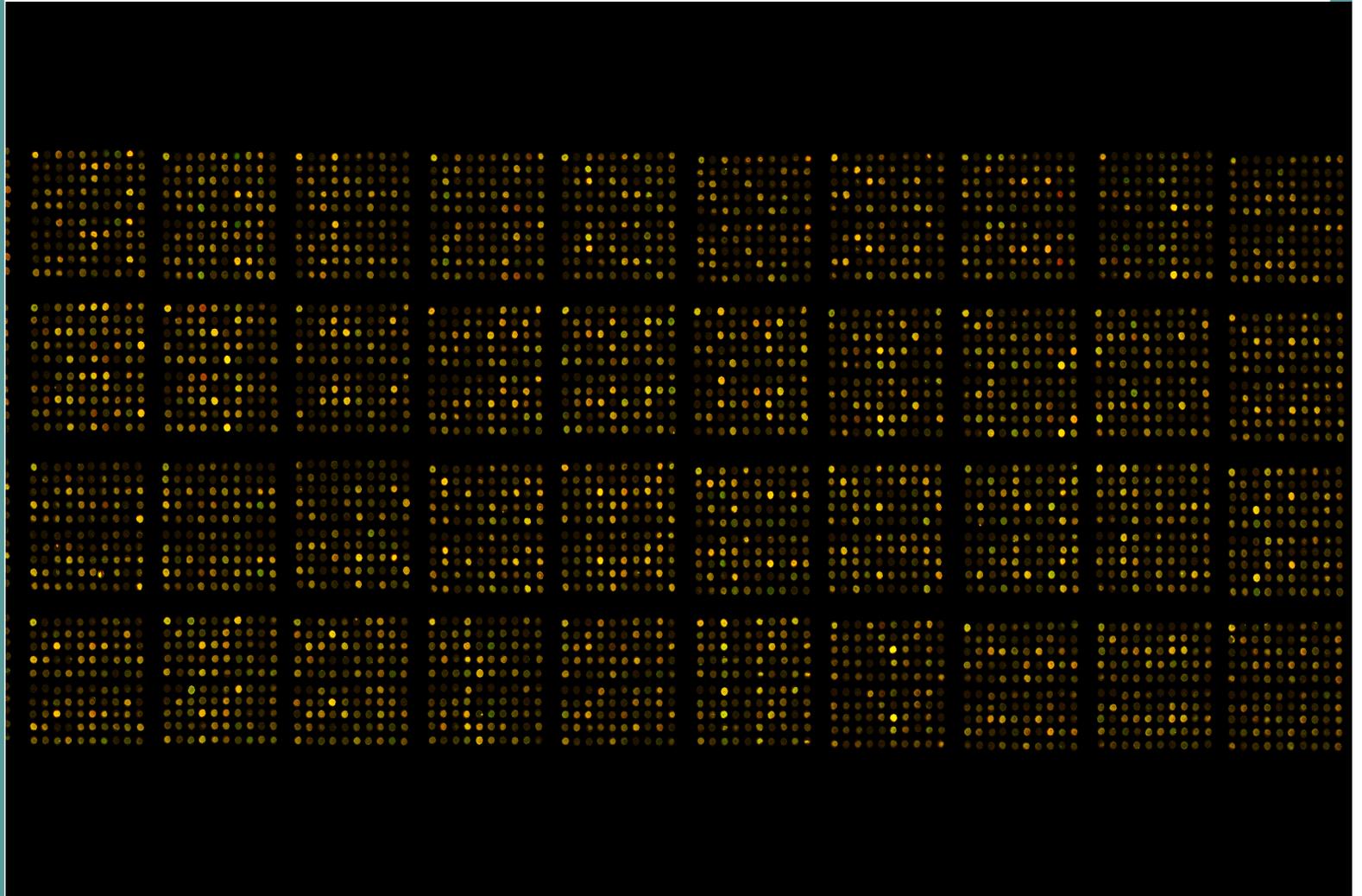
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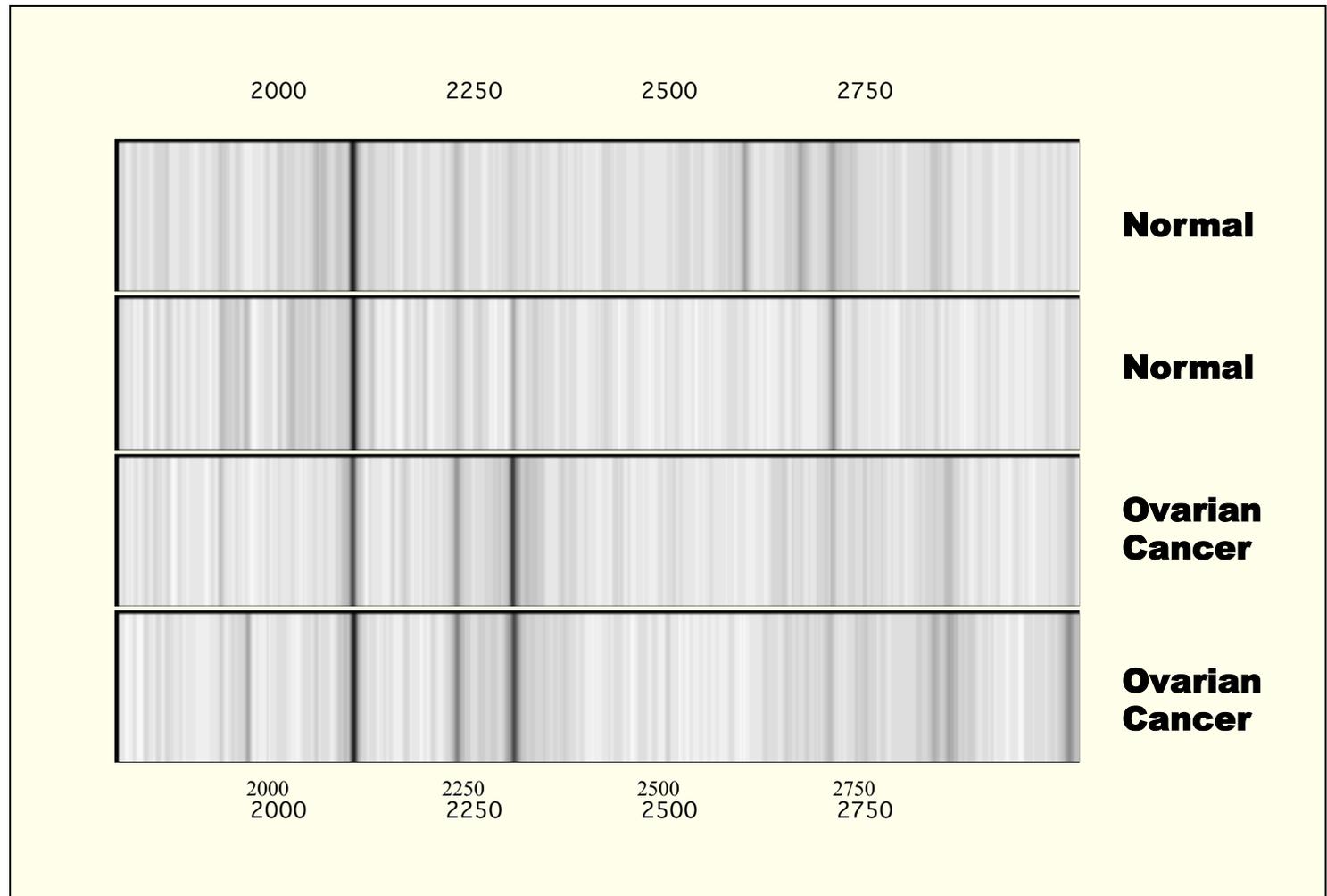
THE HUMAN GENOME



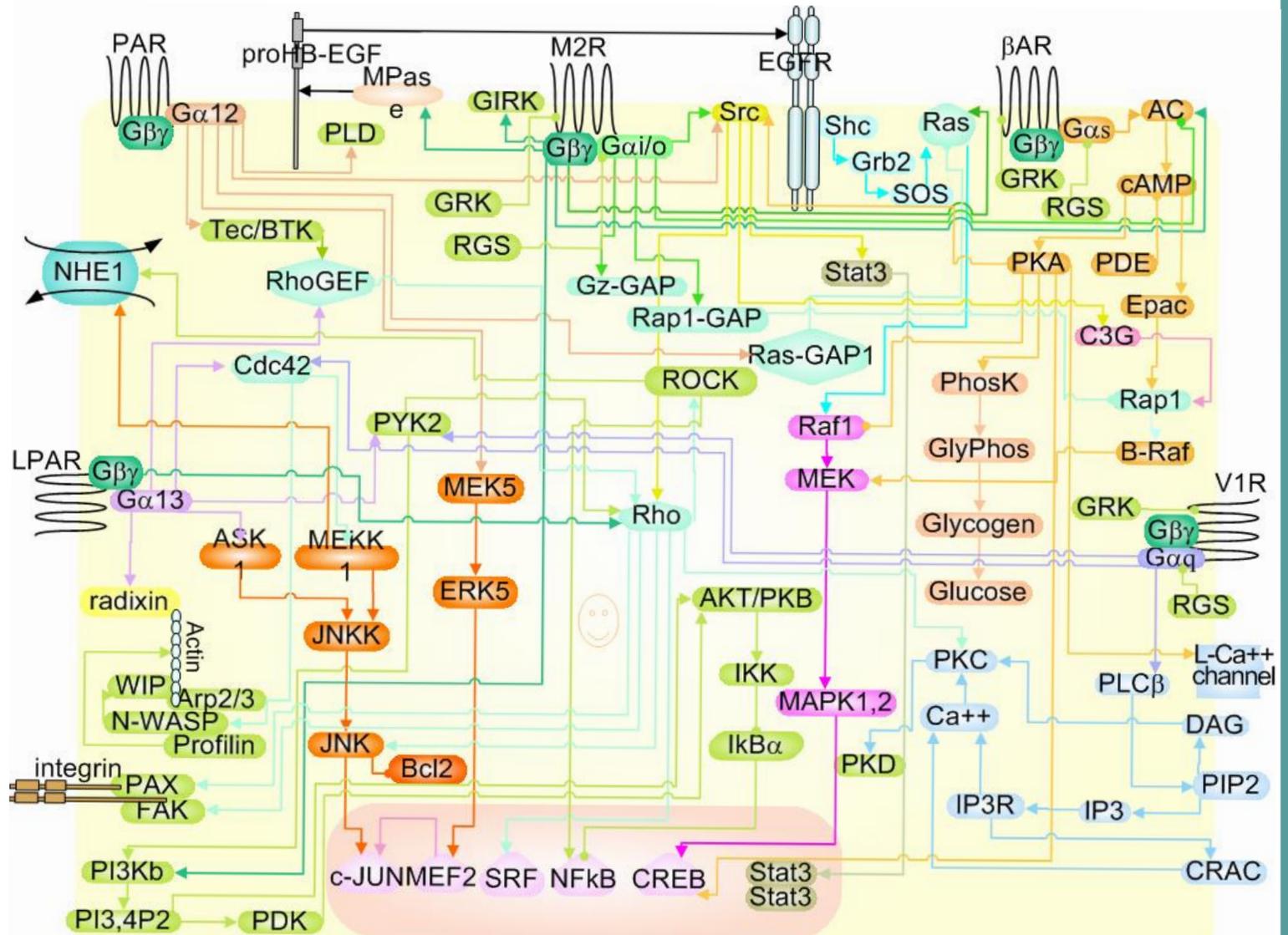
ANALYSIS OF RNA



ANALYSIS OF PROTEINS



Intracellular Signaling Pathways



SEA CHANGE

- **Comprehensive “Omic” Data**
 - High throughput DNA Sequencing
 - SNP Arrays
 - Gene Expression Arrays
 - Methylation Arrays
 - Proteomics, MS, NGS, ...
- Samples from Large Numbers of Patients Well Studied
- Biostatistical and Computational Analysis
 - Moore’s Law: Computational Computing Power doubling every 18 – 24 months

The Promise of Molecular Diagnostics

- Estimate Risk of Developing Different Kinds of Cancers
 - Individualized plans for Screening
 - Selective Use of Chemoprevention
 - Specific Recommendations Regarding Diet and Lifestyle
- Detect Disease Earlier
- Define Prognosis of Each Cancer Patient Precisely
- Predict Response to different Drugs and Modalities

The Promise of Molecular Therapeutics

- Predict Toxicity for Normal Tissues with Greater Accuracy
- Develop More Effective Curative Treatment
- Turn Cancer into a Chronic Disease
- **Treatment can be Personalized**
 - Identify Specific Defects in Cancer Cells
 - Inhibit Function of Abnormal Proteins
 - Correct Abnormal Cell Behavior
 - Identify Conventional Drugs that will Work for a Particular Patient.

Translational Research & its Community

- Clinical Oncologist deal directly with the heterogeneity of cancer every day and have been personalizing cancer care for decades
- Advances in basic and translational research will predict risk, prognosis and response with increasing accuracy
- **INSTEAD OF PRESCRIBING FOR THE AVERAGE PATIENT, WE WILL TREAT THE 'INDIVIDUAL'**
- Continued advances and medical education
 - Many more combinations of drugs
 - Pathways rather than disease sites
 - **More Computer-Based Treatment Planning**



APPARENTLY YOU'RE SUFFERING
FROM $\frac{3N - \sqrt{B}}{6 - 2T}$.

Translational Research in 21st Century : *Accelerating Personalization of Patient Care*

- Integration of Molecular Diagnostics and Therapeutics
- Collaboration of Multiple Groups
 - Academia, NCI, FDA, Pharma
- **Establish Translational Support Teams and Infrastructure**
 - Platform of common Informatics tools and Infrastructure
 - Standards – Its all about this – really !
 - Sustained Architecture
 - Interoperability between local and commercial partners

Requirements for Translational Research

- Substantial Long-Term Investment
- Establishment and Ongoing Support of Teams
 - Physician-Scientists
 - Clinical Investigators
 - Molecular Imagers
 - Molecular Pathologists
 - Translational Scientists
 - Research Nurses and Data Managers
 - Experts in Regulatory Affairs
 - Biostatisticians
 - **CLINICAL AND BIOMEDICAL INFORMATICIANS**

Requirements for Translational Research

- Large Number of Patients Uniformly Studied
 - Standard Treatment Protocols
 - Routine Pre-treatment Biopsies
 - Novel Trial Design to Study Predictive Markers for Conventional Single Agents
 - Adaptive Trials to Test Predictive Markers for Novel Agents
- **Infrastructure for Collection, Management, Preservation, and Rapid Analysis of Clinical, Biomedical, and Biospecimen data under compliant conditions**

Unified Infrastructure Needs

Leveraging Integrative Informatics Standards & Platforms to Enable High-throughput Translational Research

Academic Institutions:

“...multiple collaborating investigators working as an investigative team in order to address complex biomedical science problems...”

UCSF Translational Informatics

Mission:

Deliver Suite of Services to support translational, biomedical, and clinical research, as well as clinical care improvement.

Focus:

- Capture, Storage, Dissemination of Clinical, Biomedical, and Research Data that can easily be merged, integrated, or aggregated with other data sets.
- Development of unified technology platforms leveraging cutting-edge advances in Informatics and computing.

Scientific Strategic Goals	Corresponding Informatics Platforms
<p>Building Clinical and Translational Research Capability</p> <ul style="list-style-type: none"> ✓ Clinical research ✓ Research infrastructure ✓ Phenotyping 	<ul style="list-style-type: none"> • Micro Array Data Management • Next Generation Sequencing Data Management • Biospecimen Data Management • Unified Registry Tools • Patient Survey Systems • Clinical Trials Management Systems • Cooperative Group Trials and EDC • Automated Adverse Event Grading
<p>Enhancing Collaborations</p> <ul style="list-style-type: none"> ✓ Social networking ✓ Resource sharing ✓ Data sharing 	<ul style="list-style-type: none"> • Electronic Data Interchange tools • Lab Data Services 'aka' data bus • Clinical System "Wrapper" • Electronic Data Warehouse • Biomedical Informatics Data Marts • Organization Publications and Profile Management • Federated Data Exchange Standards
<p>Encouraging T1 Translational Research</p> <ul style="list-style-type: none"> ✓ Knowledge translation ✓ Hypothesis generation 	<ul style="list-style-type: none"> • Genome Browser • GWAS query processing • Genomic Data Analysis • Biomarker Data Analysis • Translational Data Analysis • Pathway Analysis Tools • Omic Interpretation Tools

TI bringing it together one kb at a time

- Standards, Operations, & Tools:
 - NCI CBIIT
 - Pharma and FDA
 - Commercial Partners
- Infrastructure & Security
- Clinical Research Informatics
- Biospecimen / Tissue Informatics
- Biomedical Informatics
- High Performance Computing
- Integration, Data Warehousing & Mining
- Education
 - **Enabling Real Impact & Change**



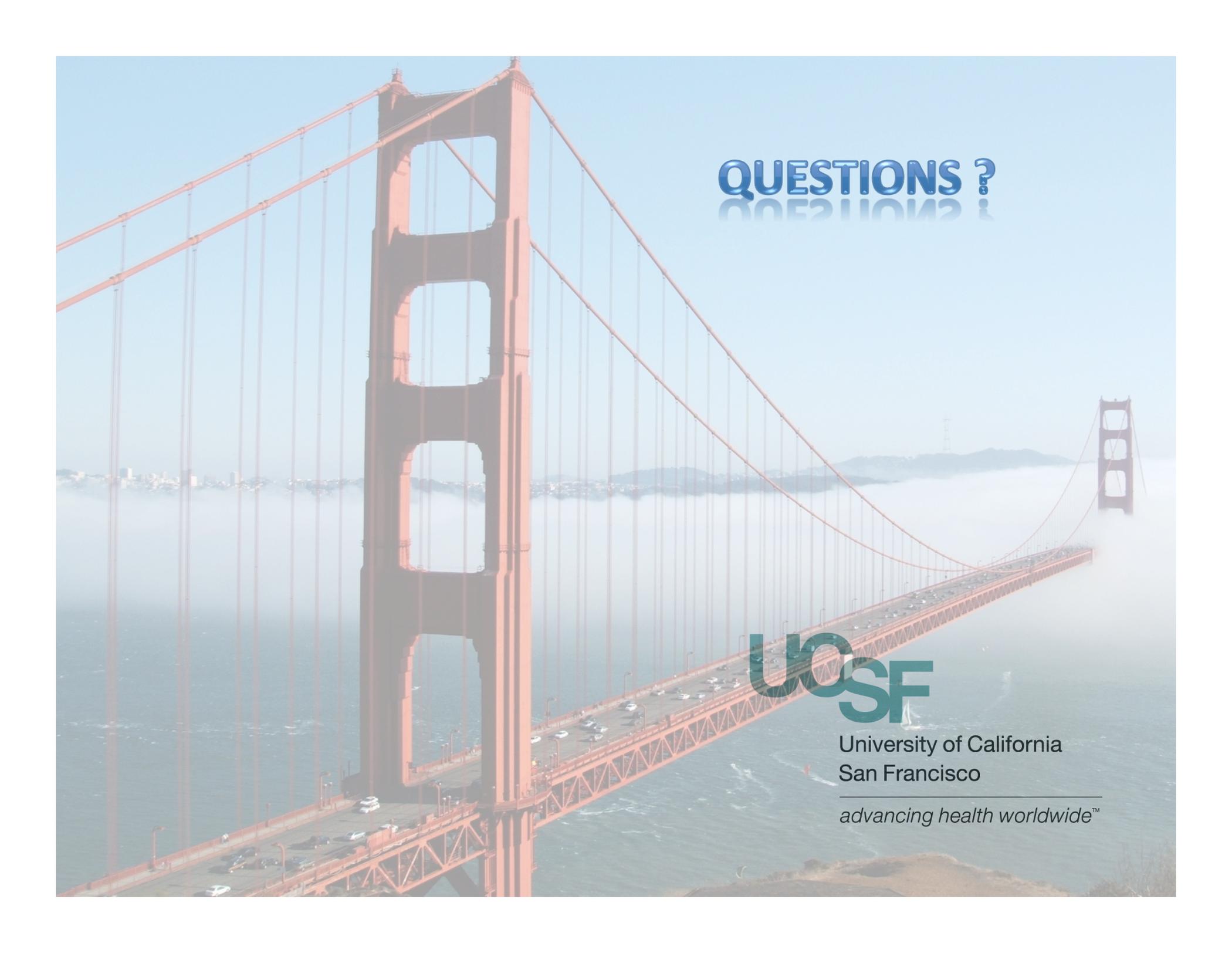
CHANGE

is good

you go first

We are not the first.. however

- UCSF : Hundreds of active open to accrual clinical research studies (T/NT) requiring such Translational Infrastructure
- Dozens bringing together
 - Genome / Phenome data
 - Adaptive Protocols
 - Multi-Site / Cooperative Group Style
 - Pharma
 - Standards

A high-angle, wide shot of the Golden Gate Bridge in San Francisco, California. The bridge's iconic orange-red towers and suspension cables are prominent against a clear blue sky. The bridge spans across the Golden Gate Strait, with the city of San Francisco visible in the distance on the left and the Marin Peninsula on the right. The water is a deep blue, and the overall scene is bright and clear.

QUESTIONS ?



University of California
San Francisco

advancing health worldwide™