An Unprecedented Era of Discovery

A transformation in medicine
“The next 10 years in biomedical research and patient care will be defined by genomics and our ability to analyze and integrate this data effectively with a patient’s phenotypic information into their actual care. It will determine how we identify and manage risk, diagnose disease and how we develop new therapies.”

John E. Niederhuber, M.D.
The Future of Cancer Care

“Personalized Cancer Medicine”

What do we mean?

• It is your personal cancer care driven by the knowledge of your unique genomic information.

• It will utilize novel information processing to create, compact, and integrate usable genomic information at point of care.
Genome sequencing suggested a new approach to treatment for twins Noah and Alexis Beery, shown here with their parents.
Alexa and her twin brother Noah

• At age 6, diagnosed with “dopa-responsive” dystonia.

• At age 13, Alexa developed severe chronic cough and difficulty breathing.

• Father is CIO at “Life Technologies” and advocated genome sequencing of the twins.

• Mutations in \textit{SPR} gene encoding the enzyme sepiapterin reductase – which enables synthesis of neurotransmitters dopamine and serotonin.
Treatment: to a dopamine precursor, doctors added 5-hydroxytryptophan, a precursor of serotonin.
TCGA: Connecting multiple sources, experiments, and data types

Three Cancers - TCGA Pilot

glioblastoma multiforme (brain)
squamous carcinoma (lung)
serous cystadenocarcinoma (ovarian)

Multiple data types
- Clinical diagnosis
- Treatment history
- Histologic diagnosis
- Pathologic status
- Tissue anatomic site
- Surgical history
- Gene expression
- Chromosomal copy number
- Loss of heterozygosity
- Methylation patterns
- miRNA expression
- DNA sequence

Biospecimen Core Resource with more than 13 Tissue Source Sites
7 Cancer Genomic Characterization Centers
3 Genome Sequencing Centers
Data Coordinating Center
The Genomics of Cancer:

Breast Cancer

Ovarian Cancer

Courtesy CWI, Netherlands

Courtesy TCGA, NCI
Kaplan-Meier Survival Curves According to EGFR Copy Number and Impact of Erlotinib

EGFR Low Copy Number

HR = .8
p = .3525

EGFR High Copy Number

HR = .43
p = .0042

Dissecting Cancer into Molecularly and Clinically Distinct Subgroups by Gene Expression Profiling
Cluster Analysis of mRNA Levels in Breast Cancer

Data courtesy of TCGA
Personalized Cancer Therapy

Today

Same Organ Site

{\begin{align*}
\text{Pt. #1} & \quad \text{#2} & \quad \text{#3} \\
\text{Standard Therapy} & \quad & \\
\end{align*}}

Future

Research
\begin{itemize}
\item Genomics
\item Proteomics
\item Immunology
\item Mechanisms
\item Rational drug design
\end{itemize}

1 in 3 Patients Benefit

\begin{align*}
\text{Therapy 1} & \quad & \text{Therapy 2} & \quad & \text{Therapy 3}
\end{align*}

INOVA HEALTH SYSTEM
The Genomics of Cancer:

- Ability to stratify organ site tumors.
- Identification of potentially key genomic alterations (Achilles heel).
- Identification of potentially critical pathways.
- Identification of targets for drug and biomarker development.
- Identify right patient for targeted therapies.
Future Cancer Therapy

Don’t forget the tumor microenvironment!

Stem Cell “like”

endothelial cells

fat

epithelium

Stem Cell

fibroblast

Macrophage/dendritic cell

TGF β

FGF

PDGF

VEGF

TGF β

FGF

VEGF

CD 8+
lymphocyte

INNOVA HEALTH SYSTEM
Wnt-Beta-Catenin Pathway is Activated in CAFs

Topflash reporter

TCFx8

luciferase

Fluc/RLuc

N3

C3
Cold Ischemia and Molecular Assay Results

HER2 IHC and FISH in Breast Cancer: Loss of Biomarker Signal with Time to Fixation

Phosphoprotein pMAPK IHC of Colon Cancer: Gain of Biomarker Signal with Time to Fixation


Hartmut Juhl, Indivumed GmbH, BRN
The Future of Health Care

Scale of Genomic Data

**Kilobyte (KB or K):**
1000 bytes

**Megabyte (MB):**
One million bytes.

**Gigabyte (GB):**
One billion bytes

**Terabyte (TB):**
One trillion bytes
Attacking Cancer

We know our assignment!

• Genomic and or proteomic markers of risk.
• Understanding behavioral/environmental causes.
• Development of preventive and risk reducing agents – screening technologies.
• Knowledge of the genomic and cellular signaling pathways involved in induction and progression.
• Novel targeted therapies.
Medical Sequencing: < $1000

—Will require ethnic specific reference genomes.

Genomic Analysis: $ ??

• Sequencing reads mapping to reference genomes.

• Candidate variant analysis. (known variants, de-novo variants, structural variants)

• Mitochondrial genome analysis.

• Large deletion analysis.

• Familial genomics. (autozygosity, x-linked inheritance, simple recessive, maternal dominant)

• Expression analysis. (epigenetics)
Admixture Analysis:

- Estimated admixture coefficients for:
  - European, African, Asian.
- Classical 3 dimensional admixture view
- Based on allele frequency data from 1000 Genomes (latest build)
In summary:

• The key to understanding cancer resides in our ability to understand the genomic drivers of risk, induction and progression of disease.

• Our research requires the highest quality of specimens.

• We should expand our tumor/host targets to include the genomically altered but stable tumor microenvironment.