Role of Genetics in Cancer Control and Public Health

individualized care through science and technology

20th Annual Maryland Council on Cancer Control Conference
November 19, 2013
Why What We Are Doing is So Important

Human and Economic Burden of Cancer

- **1,660,290** Americans will be diagnosed in 2013
- **580,350** are expected to die of cancer in 2013
- More than **1,600** people a day die from cancer
- **Cost of cancer care was $157 billion** in 2012
- Second most common cause of death

Estimated # of New U.S. Cancer Cases

<table>
<thead>
<tr>
<th>Year</th>
<th>Estimated Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>1,284,900</td>
</tr>
<tr>
<td>2009</td>
<td>1,479,350</td>
</tr>
<tr>
<td>2013</td>
<td>1,660,290</td>
</tr>
</tbody>
</table>
Cancer Cases Are Rising Globally

- Today, more than half of new cancer cases and nearly two-thirds of cancer deaths occur in the low income, lower middle income, and upper middle income countries of the developing world.

- By 2030, the developing world is expected to bear 70% of the global cancer burden.

A Transformation in Medicine

Chronic Diseases Account for >65% of Health Care Costs.

Aging Population

• The fastest growing component of the U.S. population is the age group > 75 years.

• Those > 65 years are more likely to have more than one chronic disease problem.

Life Style and Behavior

• Chronic diseases often share man-made causes – tobacco, obesity, substance abuse and inactivity.

Health Disparities

• Chronic diseases are often a greater burden in the poor and less educated population

• Access to care will be an increasing determinant of cost and of disease mortality
All-Site Cancer Death Rates by Age

Source: SEER, 2006-2010, All Races, Both Sexes
All-Site Cancer Rates in Successive Birth Cohorts by Age of Death

- Mortality rates for cancer in the U.S. have declined over past 50 years despite relatively stable incidence (except lung cancer).
- Declines suggest that better cancer detection, treatment and prevention have been effective.
- Effects may be even larger than currently observed; cancer death rates at every age have been successively lower for each generation since 1925.
- As younger groups age, their lower death rates will greatly impact (reduce) age-adjusted death rates utilized to mark our progress against cancer.

Declining U.S. Mortality Rates from 1991-2006

Rates are age-adjusted to 2000 U.S. standard population

U.S. mortality data, National Center for Health Statistics, Centers for Disease Control and Prevention, 2009
Growth in the Population of Cancer Survivors by Age

Forsythe et al., Abeloff’s Clinical Oncology 5th ed., 2013
Annual Deaths Attributed to Tobacco

Center for Disease Control and Prevention, U.S. 2000-2004
Cancer is a Disease of the Genome

- Deletions
- Amplifications
- Mutations
- Translocations
- Epigenetic changes
- Transcriptional/translational regulation

It arises from changes within the DNA of our cells during their lifespan
Mid 1980s

Photos by Len Rubenstein; courtesy of the Broad Institute

An Unprecedented Era of Discovery

A transformation in medicine
Tumors as “Organ” Systems

Tumors are more than just a mass of cancer cells.
Tumors as “Organ” Systems
Individualized Cancer Care

Today - some thoughts regarding Genomics and Cancer.

• Determining risk
• Managing risk
• Noval molecular targets
• Pharmacogenomics
• Each cancer an N of 1
Translational Science: The Paradigm Shift

The 20th Century Paradigm:
Organ site-based, single agent based trials

- Reactive
- Based on gross differences
- Toxic (MTD/DLT)
- Emerging resistance
- Poor life quality

The New Paradigm:
Multiple, highly targeted agents matched to molecularly selected patients

- Proactive
- Rational/targeted
- Less toxicity
- Biomarker endpoints (subcellular target imaging)
- Significant savings of cost and time

Research
- Human genome
- Genomics
- Proteomics
- Immunology
- Mechanisms
- Rational design
Creating the repair manual.

- Derive a functional understanding of the causal defect/dependance; e.g. Wnt, P13K, NF-kB...
  - Distinguish passenger defects from true drivers.

- Determine dependence of cancer cells and micro-environment cells on genes that are amplified, translocated, mutated or epigenetically altered.
  - “Oncogene addiction”

- Find genes to which cancer cells are addicted but that are not mutated, translocated or amplified.
  - “Non-oncogene addiction”
Kaplan-Meier Survival Curves According to EGFR Copy Number and Impact of Erlotinib

EGFR Low Copy Number

- HR = 0.8
- p = 0.3525

EGFR High Copy Number

- HR = 0.43
- p = 0.0042

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GBM: CpG Island Methylator Phenotype Linked to *IDH1* Mutation and Better Survival

- Occurs in Younger Patients
- Is a Subset of Proneural Expression Subtype
- Is Associated with Better Survival
- Is More Frequent in Low-Grade Gliomas
- Is Not Associated with *MGMT* Methylation
- Is Tightly Linked to *IDH1* Mutation

Noushmehr et al. (2010) Cancer Cell, Online
Dissecting Cancer into Molecularly and Clinically Distinct Subgroups by Gene Expression Profiling

Diffuse Large B Cell Lymphoma

Activated B Cell-like DLBCL (ABC)  Germinal Center B Cell-like DLBCL (GCB)  Primary Mediastinal B Cell Lymphoma

Genes

Lymphoma Biopsies

Probability of survival

Progression-free survival (yrs) (R-CHOP Rx)

GCB DLBCL  75%

ABC DLBCL  40%

P = 2.27 x 10^-8

High

Low

Gene Expression
Individualized Cancer Therapy

**Today**

```
Pt. #1
#2
#3
```

Standard Therapy

1 in 3 Patients Benefit

**Future**

```
Therapy 1
Therapy 2
Therapy 3
```

Research
- Genomics
- Proteomics
- Immunology
- Mechanisms
- Rational drug design
Cancer Diagnosis and Treatment

- Service offered through three commercial vendors and several academic centers.
- Used to diagnose and direct therapy based on genomic identification of biomarkers & targets.
ITMI Genomics Data Base

- WGS @ >40X of mother, father and newborn.
- SNP, CNV, SV.
- RNAseq expression, CpG methylation.
- Clinical study specific data and eHR information.
Germline Variations Impacting Cancer Predisposition.

- WGS from ancestrally-diverse cohort of 681 healthy adults – negative pers./fam. Hx.
- Profiled nonsynonymous variation in 158 genes causally implicated in cancer.
- Selected five genes for in depth analysis: BRCA1, BRCA2, KRAS, TP53, and PTEN.
Germline Variations Impacting Cancer Predisposition.

• 2,688 distinct genetic variants identified within the cohort.

• All individuals carry variants that may impact cancer susceptibility.

• Average of 68 variants per individual.

• Most variants are very rare with 75% found in only one or two individuals.

• Allele frequencies vary between ancestral groups.
Germline Variations Impacting Cancer Predisposition.
Ancestry-based subpopulations in study.

<table>
<thead>
<tr>
<th>Subpopulation</th>
<th># Individuals</th>
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<tbody>
<tr>
<td>African</td>
<td>43</td>
</tr>
<tr>
<td>African-European</td>
<td>46</td>
</tr>
<tr>
<td>Central Asian</td>
<td>50</td>
</tr>
<tr>
<td>East Asian</td>
<td>62</td>
</tr>
<tr>
<td>European</td>
<td>331</td>
</tr>
<tr>
<td>Hispanic</td>
<td>118</td>
</tr>
<tr>
<td>Other</td>
<td>31</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>681</strong></td>
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</table>
Cancer Susceptability Genes

Germline Variations Impacting Cancer Predisposition.
Cancer Susceptability Genes

Germline Variations Impacting Cancer Predisposition.
Importance of Ancestral Specific Reference Genomes in Genomic Medicine.
The Reference Genome

- The information used in whole genome sequencing to assemble a person’s sequence information into a complete genome. (ncbi37)
- The reference genome is the basis for identifying relevant variants in a person’s genome.
- It directly impacts the ability to determine the disease-causing mutations.
- The NIH reference genome is not suited to medically relevant sequencing.
Donors were recruited by advertisement in *The Buffalo News*, on Sunday, March 23, 1997. DNA was extracted from the blood of 10 male and 10 female volunteers. About 80 percent of the reference genome came from eight people and one male individual accounts for 66 percent of the total reference genome.
Pre-Term Birth: Country of Birth

- Country of Birth = 79
- Ancestry currently not used in WGS assembly
Re-distribution of Personal Variants

Common Variants

Ancestral Reference Genomes

Familial Sequencing

Personal Variants

Common Variants

Ancestral Variants

Familial Variants

Personal Variants

Probably Not Disease Causing

Potentially Disease Causing

Information Provided by Sequencing Companies

Provided by Sequencing Companies

35
Genomic Medicine Today

- Medicine in a reactive discipline, while genomic medicine focuses on prediction (risk) and prevention.

- Pharmacogenomics and cancer genomics lead the field in utility.

- Through analysis of WGS data we can screen for many actionable genomically based alterations:
  - germline cancer predisposition genes, metabolic defects, autism, childhood obesity, cardiovascular disease risk.

- Sequence banking will be common practice.
### Genomic Medicine: Pharmacogenomics

<table>
<thead>
<tr>
<th>Gene</th>
<th>Total Drugs</th>
<th>Drugs in Key Service Lines</th>
<th>Oncology Drugs</th>
<th>Cardiovascular Drugs</th>
<th>Neuroscicence Drugs</th>
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</thead>
<tbody>
<tr>
<td>CYP2D6</td>
<td>35</td>
<td>11</td>
<td>Coreg, Toprol, Rhythmol, Innopran Quinidine</td>
<td>Nuedexta, Razadyne Xanazine, Codine Ultracet</td>
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<tr>
<td>CYP2C19</td>
<td>15</td>
<td>4</td>
<td>Plavix, Effient, Brilinta</td>
<td>Onfi</td>
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<tr>
<td>TPMT</td>
<td>4</td>
<td>4</td>
<td>Platinum Purinethol Thioguanine</td>
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<td>Imuran</td>
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<tr>
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<tr>
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<td>1</td>
<td></td>
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<td>Tegretol, Dilantin</td>
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<tr>
<td>NAT1;NAT2</td>
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<td>Bidil</td>
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<td>HLA-B*5701</td>
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</table>
Pharmacogenomics

All patients with same diagnosis

Responders and patients not experiencing severe toxicity

Non-responders and toxic responders
Example: Cancer Therapies

Modified from American Association for Cancer Research.
Genomic Driven Drug Discovery

Inova Health System
The goal of individualized cancer medicine is to use genomic characterization to manage disease risk and to optimize patient therapy.