What's It All About Alphie?

The Alphabet Soup of Genetic and Genomic Testing in Cancer

TP53

EGFR

PDL1

ALK

BRCA1

MLH1

Kras

the cure is within

ABRAMSON CANCER CENTER
Conflict of Interest

No financial conflict of interest to report

Only bias – Unapologetically biased first time grandmother
Objectives

- Differentiate between somatic gene mutation and germline gene mutations
- Describe the characteristics suggesting an inherited cancer susceptibility family
- Provide an overview of high penetrant inherited cancer syndromes
- Describe the advances in gene analysis leading to identification of cancer specific markers
- Review the testing advances for genomic analysis of tumor and circulating tumor DNA
- Delineate the role of Oncology Nursing in cancer genetics and genomic testing

Source: http://www.healthypeople.gov/document/Word/Volume1/03Cancer.doc
“All Cancer is Genetic”

- A series of cellular, genetic aberrations that cause abnormal cell proliferation
- Characterized by unchecked local growth (tumor formation) and invasion of surrounding tissue
- Ability to metastasize or spread in a noncontiguous fashion to form secondary sites.
Cancer Genetics and Cancer Genomics

- **Cancer Genetics** – Single Gene Hereditary Disorders
- **Cancer Genomics** –
  - the identification of multiple genes, DNA sequences, and proteins and their interaction with one another

- changed the practice and implementation of cancer risk assessment, risk reduction, prevention, screening, diagnosis, therapeutics, and options for personalized health care

- High-throughput technologies, such as whole-genome sequencing and exome sequencing, have resulted in a shift in focus from cancer genetics to cancer genomics.
20th Century Breakthroughs Advancing Science

1953 – Watson and Crick –
Description of the DNA structure

1960 – Hungerford & Nowell
– Philadelphia Chromosome

1966 – Henry Lynch, MD – “Father of Hereditary Cancer”
describes Hereditary Nonpolyposis Colorectal Cancer (HNPCC)
1970 Alfred Knudson – Two Hit Hypothesis
Retinoblastoma as a Hereditary Cancer Syndrome

1971 – President Nixon –
“The War on Cancer”
The National Cancer Act
Mary Claire King, MD, PhD
Discovered the BRCA1 gene 1993

Michael Stratton, MD, PhD &
Richard Wooster, PhD
Discovered the BRCA2 gene 1994
The Human Genome Project – 1990 - 2003

Funded and coordinated by the US Dept of Energy & NIH
International effort blending academic and commercial research efforts

2000 – Initial draft mapping announced
2003 – Project completed – 99.9% of human genome mapped

Project Objectives
- Identify all of the genes in human DNA
- Determine the exact sequencing of 3 billion base pairs
- Develop databases to store this information
- Improve tools for data analysis
- Transfer related technologies to the private sector
- Address ethical, legal and social issues (ELSI) that may arise

More than 300 genes have been implicated in the diabolical transformation of normal cells into cancer cells, and that has led to major insights into cause, prevention, diagnosis, treatment and cure.

Francis Collins, MD, PhD, Director NIH
<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1890</td>
<td>Gene mutations described in cancer</td>
</tr>
<tr>
<td>1909</td>
<td>Immune system suppression leads to tumor development</td>
</tr>
<tr>
<td>1914</td>
<td>Chromosomal abnormalities lead to cancer; tumor suppressor genes and oncogene functions theorized</td>
</tr>
<tr>
<td>1950</td>
<td>Watson and Crick describe the Double Helix DNA structure</td>
</tr>
<tr>
<td>1960</td>
<td>Philadelphia Chromosome in CML describe – translocation of Ch 22:Ch9</td>
</tr>
<tr>
<td>1966</td>
<td>Henry Lynch, MD describes the first hereditary cancer family syndrome - HNPPC</td>
</tr>
<tr>
<td>1971</td>
<td>Alfred Knudson, MD proves the Two-Hit Hypothesis explaining difference between Inherited and Sporadic Cancer</td>
</tr>
<tr>
<td>1973</td>
<td>David Compings describes the theory of germline inheritance of mutated tumor suppressor genes</td>
</tr>
<tr>
<td>1979</td>
<td>First discovery of tumor suppressor genes – RB and TP53</td>
</tr>
<tr>
<td>1983</td>
<td>Cancer Epigenetics discoveries</td>
</tr>
<tr>
<td>1990</td>
<td>HUMAN GENOME PROJECT INITIATED</td>
</tr>
<tr>
<td>1993</td>
<td>Mary Clair King discovers the BRCA1 gene</td>
</tr>
<tr>
<td>1999</td>
<td>Cancer Profiling – distinguishing between cancer types</td>
</tr>
<tr>
<td>2001</td>
<td>Targeted Cancer Therapy – drug developed for specific targets</td>
</tr>
</tbody>
</table>
Genetic Information Non-Discrimination Act

2008 – President George W. Bush signs GINA into law

Protects the rights of individuals against discrimination in the workplace or in group health insurance based on genetic testing information.

Ensures privacy and confidentiality of genetic testing information

32 Individual states have also enacted state laws to further strengthen protection against genetic discrimination in varying levels
NCI and NHGRI funding began in 2006

- Tissue Sample Repository
- Goal – chart the genomic changes in over 20 types of cancer
- Objective – identify targets for cancer therapies, early detection and prevention of cancer
- Open and shared data portal for all researchers
By mid-1990’s, some roadmaps constructed
Cancer as a Genetic Disease

- ALL Cancer is caused by Genetic mutations
- NOT all cancers are inherited in nature

Sporadic Cancer

1. SOMATIC mutations - NOT inherited
2. Mutations found ONLY in the tumor
3. Accumulation of genetic damage over the course of a lifetime of exposures
4. Usually older age of onset – age >65
5. Social and lifestyle risk factors, environmental risk factors
6. Unlikely to see a pattern of specific cancers in family

Inherited Cancer

1. GERMLINE mutation in egg or sperm
2. Inherited from mother or father
3. Mutation found in all cells of the body
4. Cancers often occur at early age <50
5. Patterns of cancer found on multiple branches of family
Knudson’s Two Hit Hypothesis

Cancer results from the accumulation of damage to the DNA from multiple exposures over the course of a lifetime.
What Factors Contribute to Cancer?

NOT Everyone with an inherited gene mutation develops cancer

Modifier Genes
Response to DNA damage
Hormonal and reproductive risk factors
Social habits
Environmental exposure
Lifestyle – exercise, weight
The Cell Cycle

- **M** (mitosis)
- **G1** (cell growth)
- **G2**
- **S** (synthesis)
- **G0** (resting)

**Oncogenes**

**DNA repair genes**

**Tumor suppressor genes**

**REPAIRS AHEAD**

**STOP**
Regulatory Genes

Major categories of Regulatory Genes

**Tumor suppressor genes**
- The cell’s brakes for tumor growth
- Cancer arises when both brakes fail

**Oncogenes**
- Accelerates cell division
- Cancer arises when stuck in “on” mode

**DNA damage-response genes – Mismatch repair**
- The repair mechanics for DNA
- Cancer arises when both genes fail, speeding the accumulation of mutations in other critical genes
Tumor Suppressor Genes

Genes that stop, inhibit or suppress cell division

Guardian of the Genome – TP53 –
most common and most important tumor suppressor gene

Loss of Tumor Suppressor Genes –
allows cells to proliferate beyond body needs – leads to cancer growth

“Loss of function” mutation effect

Examples of loss of Tumor Suppressor Gene:

- Rb – Retinoblastoma, osteosarcoma
- P53 – Li Fraumeni Syndrome
- APC – Familial Adenomatous Polyposis
Tumor Suppressor Genes

Normal genes (prevent cancer)

1st mutation (susceptible carrier)

2nd mutation or loss (leads to cancer)
Oncogenes

ProtoOncogenes — are normal cell proliferation genes that promote cellular division during embryonic development, then turn off

Oncogenes — are altered forms of proto-oncogenes which interfere with normal cell growth, differentiation and apoptosis

“Gain of Function” or “Up-Regulation” mutation effect

Examples of Oncogene Overexpression:

- RET – Thyroid Cancers
- c-myc – Burkitt’s Lymphoma
- Ras – Sarcomas, neuroblastoma, leukemias
Oncogenes

Normal genes (regulate cell growth)

1st mutation (leads to accelerated cell division)

1 mutation sufficient for role in cancer development
DNA Repair Genes – Mismatch repair genes

Subset of Tumor Suppressor Genes that repair DNA damage caused by carcinogens

If unable to repair, signals cell apoptosis

If normal mechanisms impaired, allows abnormal cells to continue replication, leading to malignancy

Examples of DNA Repair gene disruption:

- BRCA1, BRCA2 – Breast and Ovarian Cancer
- MLH1, MSH2, MSH6 – HNPCC (Lynch Syndrome)
DNA Mismatch Repair

Base pair mismatch

Normal DNA repair

Mutation introduced by unrepaired DNA
How Much Cancer is Inherited?

The majority of all cancers are sporadic in nature.
Inherited Cancer Syndromes

- Genetic mutation passed down through generations
- Associated with specific pattern of cancers in family
- Mutation carriers have increased susceptibility to cancer – Increased risk of developing cancers
- Characteristics of family with inherited cancer syndrome:
  - Many cancers over 2-3 generations on one side of family
  - Early onset of cancer – usually under age 45-50
  - Founder mutations associated with certain ethnic groups
Pedigree Analysis

Western Europe (-AJ)

Eastern Europe (-AJ)

- Cancer.Diagnosis = Breast
- Cancer.Diagnosis = Ovarian
Autosomal Dominant Inheritance

- Each child has 50% chance of inheriting the mutation
- No “skipped generations”
- Equally transmitted by men and women

\[ \square \quad 0 \quad \text{Normal} \]
\[ \square \quad \square \quad \text{Affected} \]
Inherited Cancer Susceptibility Genes Discoveries

- Well described syndromes, defined cancer risk profile
- Evidence based risk management interventions

<table>
<thead>
<tr>
<th>Hereditary Cancer Syndrome</th>
<th>High Risk Gene</th>
<th>Discovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary Breast and Ovarian Cancer</td>
<td>TP53</td>
<td>1990</td>
</tr>
<tr>
<td></td>
<td>BRCA1</td>
<td>1993, 1994</td>
</tr>
<tr>
<td></td>
<td>BRCA2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PTEN</td>
<td>1997</td>
</tr>
<tr>
<td></td>
<td>CDH1</td>
<td>1998</td>
</tr>
<tr>
<td>Hereditary Colorectal Cancer</td>
<td>APC gene</td>
<td>1988</td>
</tr>
<tr>
<td></td>
<td>MLH1, MSH2, MSH6, PMS2 genes</td>
<td>1993</td>
</tr>
<tr>
<td></td>
<td>STK 11 genes</td>
<td>1996</td>
</tr>
<tr>
<td>Hereditary Endocrine Cancers</td>
<td>MEN 2</td>
<td>1993</td>
</tr>
<tr>
<td></td>
<td>VHL</td>
<td>1994</td>
</tr>
<tr>
<td></td>
<td>MEN 1</td>
<td>1997</td>
</tr>
<tr>
<td>Hereditary Childhood Cancers</td>
<td>Retinoblastoma – RB gene</td>
<td>1979</td>
</tr>
<tr>
<td></td>
<td>Li Fraumeni – TP53 gene</td>
<td>1979</td>
</tr>
</tbody>
</table>
Gene | Year
---|---
CHEK2 | 2002
ATM | 2006
BRIP1 | 2006
NBS1 | 2006
RAD50 | 2006
MRE11 | 2006
PALB2 | 2007

Population Frequency and Relative Risk

BRCA 1, BRCA2, TP53, PTEN, CDH1

CHEK2, PALB2, ATM
BRIP1, RAD51

## Multiplex panel testing

<table>
<thead>
<tr>
<th>Category</th>
<th>Gene</th>
<th>Ambry Cancer Next</th>
<th>Myriad myRisk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High risk breast cancer genes</strong></td>
<td>BRCA1</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>BRCA2</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>CDH1</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>PTEN</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>STK11</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>TP53</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Moderate risk breast cancer genes</strong></td>
<td>ATM</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>BRIP1</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>CHEK2</td>
<td>X</td>
<td>X</td>
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<td></td>
<td>NBN</td>
<td>X</td>
<td>X</td>
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<tr>
<td></td>
<td>PALB2</td>
<td>X</td>
<td>X</td>
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<tr>
<td></td>
<td>RAD50</td>
<td>X</td>
<td></td>
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<tr>
<td><strong>Less well understood br/ov cancer genes</strong></td>
<td>BARD1</td>
<td>X</td>
<td>X</td>
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<tr>
<td></td>
<td>MRE11A</td>
<td>X</td>
<td></td>
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<tr>
<td></td>
<td>RAD51C</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>RAD51D</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Colon cancer genes</strong></td>
<td>APC</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>BMPR1A</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>MLH1</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>MSH2</td>
<td>X</td>
<td>X</td>
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<tr>
<td></td>
<td>MSH6</td>
<td>X</td>
<td>X</td>
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<td></td>
<td>MUTYH (AR)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>PMS2</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>SMAD4</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Genes a/w other cancers</strong></td>
<td>CDK4</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>CDKN2A</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

- **NCCN guidelines exist for testing and intensive clinical management of breast and other associated cancer risks**
- **Breast cancer risks variably defined (or controversial)**
- **No guidelines for testing or management of carriers**
- **Unclear associated cancer risks**
- **Established risks and guidelines for other cancers**
- **Breast cancer risk unclear**

*Courtesy of Kara N. Maxwell, MD, PhD*

*University of Pennsylvania*
High Penetrance Inherited Cancer Syndromes

Hereditary Breast and Ovarian Cancer – BRCA1 & BRCA2
- young age of onset (<50), triple negative breast cancers
- Female breast & ovarian; Male breast, early onset prostate

Li Fraumeni Syndrome – P53 gene
- very early onset (<25-30)
- Classic – Breast, Adrenal Cortex, Sarcomas, Neuroblastoma

Lynch Syndrome (HNPCC)
- young age of onset (<50)
- Colon, uterine, ovarian, gastric, small bowel cancers

Familial Adenomatous Polyposis – FAP
- hundreds to thousands of colon polyps
Hereditary Breast and Ovarian Cancer

**BRCA1**
- Young age of onset < 40
- Triple Negative Breast Cancer
- Lifetime Risks
  - Breast Cancer 60-80%
  - Ovarian Cancer 30-45%
  - Pancreatic 2-3%

**BRCA2**
- Age of onset >40
- ER/PR+ breast cancers
- Lifetime Risks
  - Breast Cancer 60-80%
  - Ovarian Cancer 10-20%
  - Pancreatic Cancer 3-5%
  - Melanoma 3-5%
  - Prostate Cancer – younger onset and more aggressive
  - Male Breast Cancer ~6%

**Risk Reduction Measures**
- Premenopausal women –
  - Oral contraceptives to reduce ovarian cancer risk
  - Increase breast surveillance with annual Breast MRI alternate with Mammo
- Post childbearing –
  - Tamoxifen or Raloxifene for breast cancer risk reduction
  - Prophylactic bilateral salpingectomy at approximately age 40
- Any age – Prophylactic Mastectomy is a personal option
Li Fraumeni Syndrome

- **TP53 gene mutation** – “Guardian of the Genome”
  - Most powerful tumor suppressor gene
  - Also most frequently mutated gene found in tumor testing – 10-60%
  - Very rare syndrome, exceptionally young age of onset, experience 1st, 2nd, 3rd cancers

- **SBLA Pneumonic** – to remember the key diagnoses
  - **S**arcoma – typically osteosarcoma but can be any type of sarcoma
  - **B**reast Cancer – very early age onset <30 yrs old
  - **L**eukemia, **L**ung – very early age onset
  - **A**strocytoma and **A**drenal Corticoid Cancers – very rare and early age

- **Age and Gender distribution variables**
  - **Age**
    - < 10yrs old – Adrenal Cortical, Brain and Sarcoma
    - Teenagers – bone sarcoma
    - Young adults > 20 yrs old – Breast Cancer and Brain tumors
  - **Gender**
    - Males – excess of Brain, Leukemia and Stomach cancers
    - Females – excess of Adrenal Cortical, Melanoma
    - Breast cancer – 100% female – no male breast cancer associated

- **Risk Reduction Measures**
  - No well defined screening – annual MRI to evaluate for soft tissue or brain
  - Females at age 20 – annual Breast MRI and mammogram
  - Avoidance of Radiation Therapy treatment
Familial Adenomatous Polyposis (FAP)

- APC Tumor Suppressor Gene located on Chromosome 5
- Phenotype-Genotype correlations – location of the mutation on the gene determines the types of features and cancers

Physical features associated with FAP

- 100s to 1000s of adenomatous polyps in colon
  - Polyps begin in childhood
  - usually detected because of rectal bleed
  - Also polyps in duodenum, small bowel and gastric fundus which are benign
- Benign tumors – osteomas, desmoid tumors, fibromas, lipomas, cysts
- Supernumerary teeth (extra teeth)
- CHRPE – Congenital hypertrophy of retinal pigment epithelium
## Cancer Risks Associated with FAP

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>General Population Risk</th>
<th>FAP Risk</th>
<th>Type of Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>5-6%</td>
<td>~100%</td>
<td>Carcinoma</td>
</tr>
<tr>
<td>Small bowel</td>
<td>&lt;1%</td>
<td>4%-12%</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Pancreas</td>
<td>&lt;1%</td>
<td>~2%</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Thyroid</td>
<td>&lt;1%</td>
<td>1%-2%</td>
<td>Papillary thyroid carcinoma</td>
</tr>
<tr>
<td>CNS</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>Usually medulloblastoma</td>
</tr>
<tr>
<td>Liver</td>
<td>&lt;1%</td>
<td>1.6%</td>
<td>Hepatoblastoma</td>
</tr>
<tr>
<td>Bile ducts</td>
<td>&lt;1%</td>
<td>Low, but increased</td>
<td>Adenocarcinoma</td>
</tr>
</tbody>
</table>

### Risk Management

- Annual colonoscopy from age 10-15 monitoring polyp burden
- Total colectomy with J pouch creation – early adulthood if adenomatous polyps
- Annual upper endoscopy to evaluate gastric, duodenum, periampulla
- Annual physical examination and thyroid exam/ultrasound for physical features

HNPCC – Lynch Syndrome

- 4 genes on 3 chromosomes – MLH1, PMS2, MSH2, MSH6
  - Mismatch repair genes – involved in repair of damaged DNA
- Early but variable age at CRC dx (~45 yrs)
  - Few adenomas- up to 10 polyps
- Tumor sites predominately in proximal colon:
  - Right colon (ascending colon & cecum) 60%
  - Left colon (descending & sigmoid colon) 40%
- Extracolonic Cancers
  - Endometrium – 20-60% risk; mean age 46
  - Ovary – 9-12% risk; mean age 42.5
  - Stomach – 11-19% risk; mean age 56
  - Small bowel – 1-4% risk; mean age 49
  - Bile Ducts – 2-7% risk; mean age not reported
  - Urinary Tract – 4-5% risk; mean age ~55
  - Sebaceous skin tumors
  - Brain/central nervous system – 1-3% risk; mean age ~50
Lynch Syndrome

- Phenotype – Genotype correlations – location of mutation determines the types of cancer, age and lifetime risk

### NCCN Guidelines Version 2.2014
Lynch Syndrome

#### Cancer Risk Up to Age 70 Years in Individuals with Lynch Syndrome Compared to the General Population

<table>
<thead>
<tr>
<th>Cancer</th>
<th>General Population Risk</th>
<th>MLH1 and MSH2&lt;sup&gt;1,2&lt;/sup&gt;</th>
<th>MSH6&lt;sup&gt;2&lt;/sup&gt;</th>
<th>PMS2&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Risk</td>
<td>Mean Age of Onset</td>
<td>Risk</td>
</tr>
<tr>
<td>Colon</td>
<td>5.5%</td>
<td>40%-80%</td>
<td>44-61 years</td>
<td>10%-22%</td>
</tr>
<tr>
<td>Endometrium</td>
<td>2.7%</td>
<td>25%-60%</td>
<td>48-62 years</td>
<td>16%-26%</td>
</tr>
<tr>
<td>Stomach</td>
<td>&lt;1%</td>
<td>1%-13%</td>
<td>56 years</td>
<td>≤3%</td>
</tr>
<tr>
<td>Ovary</td>
<td>1.6%</td>
<td>4%-24%&lt;sup&gt;5&lt;/sup&gt;</td>
<td>42.5 years</td>
<td>1%-11%</td>
</tr>
<tr>
<td>Hepatobiliary tract</td>
<td>&lt;1%</td>
<td>1.4%-4%</td>
<td>50-57 years</td>
<td>Not reported</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>&lt;1%</td>
<td>1%-4%</td>
<td>54-60 years</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Small bowel</td>
<td>&lt;1%</td>
<td>3%-6%</td>
<td>47-49 years</td>
<td>Not reported</td>
</tr>
<tr>
<td>Brain/CNS</td>
<td>&lt;1%</td>
<td>1%-3%</td>
<td>~50 years</td>
<td>Not reported</td>
</tr>
<tr>
<td>Sebaceous neoplasms</td>
<td>&lt;1%</td>
<td>1%-9%</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Pancreas&lt;sup&gt;4&lt;/sup&gt;</td>
<td>&lt;1%</td>
<td>1%-6%</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

<sup>1</sup>Ref 412
<sup>2</sup>Ref 413
<sup>3</sup>Ref 414
<sup>4</sup>Ref 415
<sup>5</sup>Median age at diagnosis cited for colon (50.8 years) and endometrial (46.6 years).
Tumor Testing can help identify Lynch Syndrome

- **Phenotype – Genotype Correlations**
  - Tumors can provide indications that suggest Lynch Syndrome gene mutations
  - **Microsatellite Instability** – presence of 1-6 repeated sequences of DNA base pairs
  - ~95% of CRC and Uterine cancer in Lynch Syndrome are MSI High (positive)
  - Can be useful in determining whether Stage II/III CRC will benefit from 5FU chemo

Tumor Microsatellite Instability

Microsatellite Instability (MSI)

- A test performed on tumor and surrounding normal tissue to help determine whether an inherited mutation in a mismatch repair gene should be suspected.
- Inherited mutations in the mismatch repair genes MLH1, MSH2, and sometimes MSH6 associated with HNPCC can lead to MSI.

![Microsatellite Stability and Instability Graphs]

The pattern seen in the tumor tissue closely matches the pattern seen in the normal tissue. This tumor has microsatellite stability.

The pattern seen in the tumor tissue does not match the pattern seen in the normal tissue. This tumor has microsatellite instability.

Key Points to Remember:

- MSS: Microsatellite is stable; less likely a mismatch repair defect is present
- MSI-low: Some instability is present; less likely a mismatch repair defect is present
- MSI-high: Instability is increased; more likely a mismatch repair defect is present
- Approximately 20% of sporadic colon cancers have MSI-high results

Courtesy of Jessica Booker, Ph.D. and McLendon Laboratories at UNC-Chapel Hill
**Tumor Immunohistochemistry (IHC)**

**Immunohistochemistry (IHC)**

IHC is a test that can be performed on tumor tissue to determine if a specific protein is expressed.

Can be performed on tissue, such as colon tumors, to look for expression of the MLH1, MSH2, PMS2, and MSH6 proteins.

**Key Points to Remember:**

- Absence of protein expression suggests a gene mutation
- Allows for a targeted approach to genetic testing
- Normal protein expression does not rule out the presence of a gene mutation

The brown staining shows the presence of the MSH2 protein.

The lack of staining shows the absence of the MLH1 protein.

*Courtesy of Leigh B. Thorne, MD and William K. Finkhouser, MD, Ph. D. at UNC-Chapel Hill*
When to Suspect a Hereditary Cancer Syndrome

- Cancer in 2 or more close relatives (on same side of family)
- Early age at diagnosis (typically < age 50)
- Multiple primary tumors in one individual
- Bilateral or multiple rare cancers
- Constellation of tumors consistent with specific cancer syndrome (e.g., breast and ovary)
- Certain tumor markers or types of histopathology
- Number and types of colon or gastric polyps
- Physical features characteristic of certain syndromes, i.e., large head circumference, freckling, skin lesions
- Evidence of autosomal dominant transmission – evaluation of a 3 generation family pedigree with evidence of cancers
- Certain ethnic ancestry – Ashkenazi Jewish
SOMATIC mutations in cells

Cancer as a disease of the aging process –
- Cellular changes or mutations accumulate over time
- Alterations in DNA repair mechanisms
- Change in target tissue proliferative activity
- Alterations in immune function
  - > age = < immune response = < Tcell production

Cancer Genomics - the identification of multiple genes, DNA sequences, and proteins and their interaction with one another
Tumor Profiling – Molecular Markers

Evaluates the **somatic** changes of a particular cancer:

- Prognostic Information
- Predictive Information
- Treatment responsiveness
- Targeted Therapies
Technology Advances Enabling Analysis

From Microscope to Microarray to NextGen Sequencing
Methods of Somatic Tumor Analysis

- **Karyotype of tumor cells**
- **Pathology analysis of tumor cells**
  - Hormone receptors
  - IHC staining for a variety of tumor markers
  - Particular features of tumor cells – lymphovascular invasion, grading
- **Microarray analysis**
  - Evaluating the DNA expression of the cancer cells in the tumor
  - Defined grid used to identify presence of specific DNA fragments
- **Next Generation Sequencing**
  - Evaluating the actual genetic code for all types of mutations
    - Will identify somatic mutations and possibly germline mutations
  - Performed on
    - Actual tumor cells and normal tissue
    - “Cell free” circulating tumor cells in blood sample, or pleural fluid
Epigenetic pathways contributing to science

- **Shedding of ERBB2**
  (Scaltriti et al., J Nat Cancer Inst, 2007)

- **Hyperactivation of PI3K/Akt by loss of PTEN and PIK3CA mutation**
  (Eichorn et al., Cancer Res, 2009)

- **Overexpression of MUC4/MUC1**
  Steric hindrance of trastuzumab binding
  (Nagy et al., Cancer Res. 2005)

- **Increase in p-ERBB3**
  (Sergina et al., Nature, 2007)

- **Cyclin E amplification/overexpression**
  (Scaltriti et al., PNAS 2011)

- **Δ16HER2 splice isoform**
  (Mitra et al., Mol Cancer Ther, 2009)

- **Activation of EPO receptor by rHuEPO**
  (Liang et al., Cancer Cell 2010)

- **Upregulation of IGF-IR receptor**
  (Gail Phillips, AACR, 2009)

- **Activation of AXL**
  (Liu et al., Cancer Res, 2009)

- **Upregulation of MET receptor**
  (Shattuck et al., Cancer Res, 2008)

- **Expression of ER**
  (Xia et al., PNAS, 2006)

Updated from: Chen et al; Clin Cancer Res; 2008
Understanding the biology of cancer controls
Karyotype analysis – Philadelphia Chromosome

Chronic Myelogenous Leukemia – Bcr-Abl gene

- Target for Gleevec
- Prognostic marker for disease remission and relapse
Onco
type DX™ 21-Gene Recurrence Score (RS) Assay

16 Cancer and 5 Reference Genes From 3 Studies

**PROLIFERATION**
- Ki-67
- STK15
- Survivin
- Cyclin B1
- MYBL2

**ESTROGEN**
- ER
- PR
- Bcl2
- SCUBE2

**INVASION**
- Stromelysin 3
- Cathepsin L2

**REFERENCE**
- Beta-actin
- GAPDH
- RPLPO
- GUS
- TFRC

**GSTM1**

**BAG1**

**CD68**

**RS**
\[
RS = + 0.47 \times \text{HER2 Group Score} - 0.34 \times \text{ER Group Score} + 1.04 \times \text{Proliferation Group Score} + 0.10 \times \text{Invasion Group Score} + 0.05 \times \text{CD68} - 0.08 \times \text{GSTM1} - 0.07 \times \text{BAG1}
\]

**Category**

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<tr>
<td>Int risk</td>
<td>RS ≥ 18 and &lt; 31</td>
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<td>High risk</td>
<td>RS ≥ 31</td>
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Oncotype DX Breast Recurrence Score

The Breast Recurrence Score result provides an individualized picture of the patient’s unique tumor biology in node-negative patients.¹⁻²

**LOW RISK**
- GROUP AVERAGE: 6.8%
- 95% CI: 4.0%–9.6%

**INTERMEDIATE RISK**
- GROUP AVERAGE: 14.3%
- 95% CI: 8.3%–20.3%

**HIGH RISK**
- GROUP AVERAGE: 30.5%
- 95% CI: 23.6%–37.4%

**RATE OF DISTANT RECURRENCE AT 10 YEARS (%)**

**RECURRANCE SCORE RESULT**

**LOW RECURRENCE SCORE DISEASE**
- INDOLENT
- HORMONE-THERAPY SENSITIVE
- LITTLE TO NO CHEMOTHERAPY BENEFIT

**HIGH RECURRENCE SCORE DISEASE**
- AGGRESSIVE
- LESS SENSITIVE TO HORMONE THERAPY
- LARGE CHEMOTHERAPY BENEFIT
Figure 1. Depicted is how the genes in 70-gene tumor expression profile are involved in the six well-defined hallmarks of cancer, in tumor progression and metastasis related biological processes, as well as epithelial-mesenchymal transition. Adapted from Cell, 100, Hanahan D, Weinberg RA., The Hallmarks of Cancer, 57–70, Copyright (2000) with permission from Elsevier.
The 70-Gene Assay (MammaPrint®) Provides a High Risk or Low Risk Result

van’t Veer et al., Nature 415, p. 530-536, 2002
Foundation Medicine – Genomic Tumor Profiling

Foundation One
- Solid tumors
- Identifies genomic alterations in 315 cancer related genes assayed

Foundation One Heme
- Somatically altered genes in Leukemia, Lymphoma, Myelomas and Sarcomas
- DNA sequencing of 406 genes
- RNA sequencing of 265 common rearranged genes
- Outlines targeted therapies that may be relevant based on those genomic alterations in patients tumor type and other tumor types
- Relevant clinical trials available

<table>
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<tr>
<th>Genomic Alterations Detected</th>
<th>FDA Approved Therapies (in patient’s tumor type)</th>
<th>FDA Approved Therapies (in another tumor type)</th>
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<td>GATA2</td>
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Foundation One – 315 cancer related genes plus introns from 28 genes often rearranged or altered in solid tumor cancers, performed on tumor tissue from biopsy or excision containing at least 20% malignant cells, TAT 14 days.
<table>
<thead>
<tr>
<th>Genomic Alterations</th>
<th>Allele Frequency</th>
<th>FDA-Approved Therapies (in patient’s tumor type)</th>
<th>FDA-Approved Therapies (in another tumor type)</th>
<th>Potential Clinical Trials</th>
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<tr>
<td><strong>EGFR</strong> exon 19 deletion (L747_A750&gt;P)</td>
<td>31.9%</td>
<td>None</td>
<td>Afatinib&lt;br&gt;Cetuximab&lt;br&gt;Erlotinib&lt;br&gt;Gefitinib&lt;br&gt;Lapatinib&lt;br&gt;Osimertinib&lt;br&gt;Panitumumab</td>
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<tr>
<td><strong>PTEN</strong> splice site 489_492+1delAAA GG</td>
<td>27.8%</td>
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<td>Everolimus&lt;br&gt;Temsirolimus</td>
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<td><strong>RET</strong> amplification - equivocal</td>
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<td>Cabozantinib&lt;br&gt;Lenvatinib&lt;br&gt;Ponatinib&lt;br&gt;Regorafenib&lt;br&gt;Sorafenib&lt;br&gt;Sunitinib&lt;br&gt;Vandetanib</td>
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# Genomic Alterations

<table>
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<tr>
<th>Gene</th>
<th>Alteration</th>
<th>Interpretation</th>
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| **EGFR** | exon 19 deletion (L747_A750→P) | **Gene and Alteration:** EGFR encodes the epidermal growth factor receptor, which belongs to a class of proteins called receptor tyrosine kinases. In response to signals from the environment, EGFR passes biochemical messages to the cell that stimulate it to grow and divide. The EGFR mutation seen here is a deletion in exon 19, encoding a portion of the kinase domain of EGFR; such mutations have been shown to activate the tyrosine kinase activity of EGFR and to confer sensitivity to EGFR tyrosine kinase inhibitors such as erlotinib and gefitinib.  
**Frequency and Prognosis:** EGFR mutations are particularly frequent in lung adenocarcinomas (35%), and have also been observed in colorectal (3%), stomach (4%), and prostate (3%) adenocarcinomas (COSMIC, Nov 2015). The Cancer Genome Atlas project reports EGFR amplification in a number of adenocarcinomas, with the highest incidence in lung (10%), stomach (6%), and cervical (2%) adenocarcinomas, and in <1% of prostate and colorectal adenocarcinomas and ovarian serous cystadenocarcinomas (cBioPortal, Nov 2015).  
**Potential Treatment Strategies:** EGFR activating mutations or amplification may predict sensitivity to EGFR inhibitors including erlotinib, gefitinib, afatinib, osimertinib, cetuximab, panitumumab, and lapatinib. Other EGFR-targeted therapies are also in clinical trials. A Phase 2 trial of the pan-ERBB inhibitor dacomitinib in patients with lung adenocarcinoma reported 98% (44/45) disease control (partial response (PR) or stable disease), including a 76% PR rate, in patients with EGFR exon 19 deletions or the L858R mutation; lower disease control and PR rates were reported in patients with other EGFR mutations, wild-type EGFR, or unknown EGFR status. Irreversible EGFR inhibitors, as well as HSP90 inhibitors, may be appropriate for patients with de novo or acquired resistance to (prior) EGFR-targeted therapy. Nectumumab is an anti-EGFR antibody that is approved to treat metastatic squamous NSCLC in combination with gemcitabine and cisplatin. The reovirus Reolysin, which targets cells that harbor activated RAS signaling due to alterations in RAS genes or upstream activators such as EGFR, is also in clinical trials in some tumor types. Reolysin has demonstrated mixed clinical efficacy, with the highest rate of response reported for head and neck cancer. |
| **PTEN** | splice site 489_492+1delAAAGG | **Gene and Alteration:** PTEN encodes an inositol phosphatase that functions as a tumor suppressor by negatively regulating the PI3K-AKT-mTOR pathway; loss of PTEN can lead to uncontrolled cell growth and suppression of apoptosis. PTEN alterations that disrupt the N-terminal PIP2 binding motif, the phosphatase domain (amino acids 14-185), and the C2 domain (amino acids 190-350) and/or C-terminal region, such as observed here, are predicted to cause a loss of function. Mutations in PTEN underlie several inherited disorders collectively termed PTEN hamartoma tumor syndrome (PHTS), which includes Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome (BRRS), PTEN-related Proteus syndrome (PS), and Proteus-like syndrome. The mutation rate for PTEN in these disorders ranges from 20-85% of patients. |
Dissemination of Tumor Cells

1. Primary Tumor Angiogenesis Invasion
2. Intravasation
   - Circulating Tumor Cell (CTC)
   - Circulating Tumor Microembolus (CTM)
3A. Extravasation (CTC)
3B. Intravascular proliferation (CTM)
4. Tumor cell Proliferation Angiogenesis
5. Metastasis
   - Mesenchymal to Epithelial Transition (MET)
   - Disseminated Tumor Cells (DTC) Micrometastases Dormancy

To bone-marrow and other organs

Release and Extraction of cfDNA from Blood

Crowley E. Nat Rev Clin Oncol 2013

Penn Medicine

Abramson Cancer Center
### Foundation ACT – Circulating Tumor DNA assay

- **Blood based ctDNA assay**
  - 62 most druggable cancer related genes
  - using Next Generation Sequencing (NGS) assay
- **Procedure** - 2 tubes of blood, result within 14 days

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<thead>
<tr>
<th>ABL1</th>
<th>CDK4</th>
<th>FGFR1</th>
<th>JAK2</th>
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**Rearrangements/Fusions (6 genes)**

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<th>ROS1</th>
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</table>

*The cure is within ABRAMSON CANCER CENTER*
Foundation ACT testing results

Patient Name
Tumor Type

Date of Birth
Sex
FMI Case #
Medical Record #
Specimen ID
Medical Facility
Ordering Physician
Additional Recipient
Medical Facility ID #
Pathologist
Specimen Received
Date of Collection
Specimen Type

Gene and Alteration: EGFR encodes the epidermal growth factor receptor, which belongs to a class of proteins called receptor tyrosine kinases. In response to signals from the environment, EGFR passes biochemical messages to the cell that stimulate it to grow and divide. The EGFR mutation seen here is a deletion in exon 19, encoding a portion of the kinase domain of EGFR; such mutations have been shown to activate the tyrosine kinase activity of EGFR and to confer sensitivity to EGFR tyrosine kinase inhibitors such as erlotinib and gefitinib.

Frequency and Prognosis: EGFR mutations are particularly frequent in lung adenocarcinomas (35%), and have also been observed in colorectal (3%), stomach (4%), and prostate (3%) adenocarcinomas (COSMIC, Nov 2015). The Cancer Genome Atlas project reports EGFR amplification in a number of adenocarcinomas, with the highest incidence in lung (10%), stomach (6%), and cervical (2%) adenocarcinomas, and in <1% of prostate and colorectal adenocarcinomas and ovarian serous cystadenocarcinomas.

Potential Treatment Strategies: EGFR activating mutations or amplification may predict sensitivity to EGFR inhibitors including erlotinib, gefitinib, afatinib, osimertinib, cetuximab, panitumumab, and lapatinib. Other EGFR-targeted therapies are also in clinical trials. A Phase 2 trial of the pan-ERBB inhibitor dacomitinib in patients with lung adenocarcinoma reported 96% (44/45) disease control (partial response or stable disease), including a 76% PR rate, in patients with EGFR exon 19 deletions or the L858R mutation; lower disease control and PR rates were reported in patients with other EGFR mutations, wild-type EGFR, or unknown EGFR status. Invertible EGFR inhibitors, as well as HSPO inhibitors, may be appropriate for patients with de novo or acquired resistance to (prior) EGFR-targeted therapy. Necitumumab is an anti-EGFR antibody that is approved to treat metastatic squamous NSCLC in combination with gemcitabine and cisplatin.

The neurexins Reoilsyn, which targets cells that harbor activated RAS signaling due to alterations in RAS genes or upstream activators such as EGFR, PTEN, is also in clinical trials in some tumor types. Reoilsyn has demonstrated minimal clinical efficacy, with the highest rate of response reported for head and neck cancer.

Tumor Type: Unknown Primary Cancer (NOS)

4 genomic alterations
15 therapies associated with potential clinical benefit
0 therapies associated with lack of response
12 clinical trials

Genomic Alterations Identified

- **EGFR** exon 19 deletion (L747_A750>P)
- **PTEN** splice site 489_492+1delAAAGG
- RET amplification–equivocal
- TP53 M237I–equivocal, splice site 672+1G>T

For a complete list of the genes assayed and performance specifications, please refer to the Appendix.

See Appendix for details.
Guardant Laboratories – Guardant 360

- Cell free DNA (cfDNA) – circulating tumor cells detected in blood
- Procedure – NGS liquid based biopsy for advanced cancer
- Tests for all national guideline recommended somatic genomic targets in SOLID tumors
- Not indicated for: heme malignancies, early stage cancers, stable disease or currently on chemo or radiation therapy

### 73-Gene Panel

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<thead>
<tr>
<th>Point Mutations (SNVs) (73 Genes)</th>
<th>Indels (23 Genes)</th>
<th>Amplifications (CNVs) (18 Genes)</th>
<th>Fusions (6 Genes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKT1, ALK, APC, AR, ARAF, ARID1A, ATM</td>
<td>ATM, APC</td>
<td>AR, BRAF, ALK</td>
<td></td>
</tr>
<tr>
<td>BRAF, BRCA1, BRCA2, CCND1, CCND2, CCNE1, CDH1, CDK4, CDK6, CDKN2A, CTNNB1, DDR2, EGFR, ERBB2</td>
<td>ARID1A, BRCA1</td>
<td>CCND1, CCND2, FGFR2</td>
<td></td>
</tr>
<tr>
<td>CDK4, CDK6, CDKN2A, CTNNB1, DDR2, EGFR, ERBB2</td>
<td>BRCA2, CDH1</td>
<td>CCNE1, CDK4, FGFR3</td>
<td></td>
</tr>
<tr>
<td>ESR1, EZH2, FBXW7, FGFR1, FGFR2, FGFR3, GATA3, CDKN2A, EGFR, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH1, IDH2, JAK2, JAK3, KIT, KRAS, MAP2K1, MAP2K2, MAPK1, KIT, MET, MLH1, MPL, M TOR, MYC, NF1, NFE2L2, NOTCH1, N PM1, N RAS, N TRK1, N TRK3, PDGFRA, PIK3CA, PTEN, PTPN11, RAF1, RB1, RET, RHEB, RHOA, RIT1, ROS1, SMAD4, SMO, STK11, TERT**</td>
<td>ERBB2, GATA3, KIT, MET</td>
<td>ERBB2, FGFR1, KIT, RET, ROS1</td>
<td></td>
</tr>
<tr>
<td>PIK3CA, PTEN, PTPN11, RAF1, RB1, RET, RHEB, RHOA, RIT1, ROS1, SMAD4, SMO, STK11, TERT**</td>
<td>SMAD4, STK11</td>
<td>PIK3CA, RAF1</td>
<td></td>
</tr>
<tr>
<td>TP53, TSC1, VHL</td>
<td>TP53, TSC1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VHL</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Exons selected to maximize detection of known somatic mutations. List available upon request.
Guardant 360 reporting

### Alteration and Therapy List

#### Summary of Somatic Alterations & Associated Treatment Options
The percentage of altered cell-free DNA (% cfDNA) circulating in blood is related to the unique tumor biology of each patient. Factors that may affect the % cfDNA of detected somatic alterations include tumor growth, turn-over, size, heterogeneity, vascularization, disease progression, and treatment.

<table>
<thead>
<tr>
<th>Alteration</th>
<th>Mutation Trend</th>
<th>% cfDNA or Amplification</th>
<th>FDA Approved in Indication</th>
<th>Available for Use in Other Indications</th>
<th>Clinical Drug Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Relevant for Therapy Selection</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EGFR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L858R</td>
<td></td>
<td>0.3</td>
<td>Afatinib&lt;br&gt;Erlotinib&lt;br&gt;Gefitinib</td>
<td>None</td>
<td>Trials Available</td>
</tr>
<tr>
<td>T790M</td>
<td></td>
<td>0.25</td>
<td>Osimertinib&lt;br&gt;Lack of Response: Erlotinib&lt;br&gt;Gefitinib</td>
<td>Afatinib</td>
<td>Trials Available</td>
</tr>
<tr>
<td>C797S</td>
<td></td>
<td>0.1</td>
<td>Erlotinib&lt;br&gt;Lack of Response: Osimertinib</td>
<td>None</td>
<td>Trials Available</td>
</tr>
<tr>
<td><strong>TP53</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y220C</td>
<td></td>
<td>0.3</td>
<td>None</td>
<td>None</td>
<td>Trials Available Nearby</td>
</tr>
</tbody>
</table>

| **Additional Alterations** | | | | | |
| **EGFR** | | | | | |
| L392M | | 0.4 | The functional consequences and clinical significance of this gene variant are not established. Similar to other alterations in circulating cfDNA, the amount (% cfDNA) of this variant may reflect disease progression or response to treatment; clinical correlation is advised. | | |

For a more detailed Guardant360 Patient Report, log onto: [https://portal.guardanthealth.com](https://portal.guardanthealth.com) or to set up an account, contact Client Services: **855.698.8887**
Guardant 360 tumor response map

- Over time and course of treatment, additional blood samples can be tested to evaluate the detectable levels of cfDNA to evaluate response to treatment

Open Access: Guardant Health website: http://www.guardanthealth.com/guardant360/#reports
Examples of Case studies

Our case studies

Breast Cancer  |  Lung Cancer  |  Melanoma

Melanoma Case Study
How Guardant360 helped a patient fight melanoma

Month 1
Hepatic core needle biopsy was QNS

Month 1
Guardant360 finds BRAF V600E

Month 1
Vemurafenib initiated

Month 2
Patient responded favorably

Breast Cancer  |  Lung Cancer  |  Melanoma

Lung Cancer Case Study
How Guardant360 helped a patient fight non-small cell lung cancer

Month 1
Tissue biopsy insufficient for genotyping

Month 1
Avoiding repeat biopsy, Guardant360 identified EGFR L858R, an actionable mutation

Month 2
First-line treatment initiated with Erlotinib

Month 4
CT scan demonstrated partial response and EGFR L858R, not detected in ctDNA

Open Access: Guardant Health website: http://www.guardanthealth.com/guardant360/#reports
Molecular Targets for Targeted Therapies

- Hormone Therapies
- Signal Transduction inhibitors
- Gene Expression modulation
- Apoptosis inducers
- Angiogenesis inhibitors
- Immunotherapies
- Monoclonal antibodies
Targeted Therapies based on Tumor Markers

- Bevacizumab
- Alemtuzumab
- Gefitinib
- Erlotinib HCl
- Cetuximab
- Her1 receptor
- CD52
- PKC-alpha
- ISIS 3521
- 26S proteasome
- Bortezomib
- Oblimersen sodium
- Bcl2
- Her1 receptor
- Trastuzumab
- Erb2 & Her2
- VEGF
- VEGF receptor
- Bcr-Abl
- CD20
- Rituxumab
- CD20

Penn Medicine

the cure is within

ABRAMSON CANCER CENTER
<table>
<thead>
<tr>
<th>Organ</th>
<th>Cancer</th>
<th>Biomarker and mechanism</th>
<th>Assay for measurement</th>
<th>Associated target and drug</th>
<th>Approximate proportion of positive tests</th>
<th>Stage of clinical validation</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>Breast cancer</td>
<td>HER2: oncogene overexpression</td>
<td>ISH, IHC</td>
<td>HER2: trastuzumab, pertuzumab, ado-trastuzumab emtansine</td>
<td>18-20%</td>
<td>In clinical use</td>
<td>(8-10)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ER/PR: suggests sensitivity to endocrine therapy</td>
<td>IHC, LBA</td>
<td>ER: endocrine therapy (tamoxifen, aromatase inhibitors)</td>
<td>75%</td>
<td>In clinical use</td>
<td>(71)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Colorectal cancer</td>
<td>KRAS: mutations activate RAS-RAF-MEK pathway and resistance to EGFR therapy</td>
<td>PCR</td>
<td>EGFR: cetuximab, panitumumab</td>
<td>40% mutated</td>
<td>In clinical use</td>
<td>(11,72)</td>
</tr>
<tr>
<td></td>
<td>GIST</td>
<td>KIT: mutation leads to constitutitional activation</td>
<td>IHC</td>
<td>BCR-ABL: imatinib</td>
<td>95%</td>
<td>In clinical use</td>
<td>(73)</td>
</tr>
<tr>
<td></td>
<td>Esophago-gastric adenocarcinoma</td>
<td>HER2: oncogene overexpression</td>
<td>ISH, IHC</td>
<td>HER2: trastuzumab</td>
<td>7-22%</td>
<td>In clinical use</td>
<td>(70)</td>
</tr>
<tr>
<td>Hematological</td>
<td>Chronic myeloid leukemia</td>
<td>BCR-ABL: balanced t(9;22) leading to the formation of a constitutively active tyrosine kinase</td>
<td>Cytogenetics, FISH, RT-PCR</td>
<td>BCR-ABL: imatinib, dasatinib, nilotinib</td>
<td>&gt;90%</td>
<td>In clinical use</td>
<td>(74)</td>
</tr>
<tr>
<td></td>
<td>Acute promyelocytic leukemia</td>
<td>PML-RARA: balanced t(15;17) leading to aberrant retinoic acid</td>
<td>Cytogenetics, FISH, RT-PCR</td>
<td>PML-RARA: All-trans retinoic acid</td>
<td>&gt;90%</td>
<td>In clinical use</td>
<td>(75)</td>
</tr>
<tr>
<td>Lung</td>
<td>NSCLC</td>
<td>EGFR (HER1): mutations in tyrosine kinase domain</td>
<td>Sequencing, ISH</td>
<td>EGFR: Erlotinib, gefitinib, afatinib</td>
<td>15% adenocarcinomas in USA (higher in Asians, women and nonsmokers)</td>
<td>In clinical use</td>
<td>(76)</td>
</tr>
<tr>
<td></td>
<td>Lung adenocarcinoma</td>
<td>ALK: Inversion in chromosome 2 leads to EML4-ALK fusion oncogene</td>
<td>FISH (IHC)</td>
<td>ALK: crizotinib, ceritinib (alecetinib under development)</td>
<td>4% (mostly adenocarcinoma)</td>
<td>In clinical use</td>
<td>(77)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multiple genes:</td>
<td></td>
<td></td>
<td></td>
<td>Continued validation</td>
<td>(49)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BRAF (V600E and non-V600E)</td>
<td>Multiplex sequencing</td>
<td>BRAF: AZD6244</td>
<td>2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>EGFR (HER1): mutations in tyrosine kinase domain</td>
<td></td>
<td>EGFR: erlotinib, gefitinib, afatinib, cetuximab</td>
<td>17%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HER2: oncogene overexpression</td>
<td></td>
<td>HER2: decinutubub, neratinib, lapatinib, trastuzumab</td>
<td>3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>KRAS: mutations activate RAS-RAF-MEK pathway and resistance to EGFR therapy</td>
<td></td>
<td>KRAS: erlotinib, tivantinib, everolimus, ridaforalimus, AZD6244</td>
<td>25%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ALK: inversion in chromosome 2 leads to EML4-ALK fusion oncogene</td>
<td></td>
<td>ALK: crizotinib, ceritinib</td>
<td>8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>MET</td>
<td></td>
<td>MET: cizotinib</td>
<td>&lt;1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>Melanoma</td>
<td>BRAF V600: 80-90% V600E mutation, a downstream mediator of RAS, leads to downstream activation of MEK and ERK</td>
<td>Sequencing</td>
<td>BRAF: vemurafenib, dabrafenib</td>
<td>40-60%</td>
<td>In clinical use</td>
<td>(78)</td>
</tr>
</tbody>
</table>

HER2, human epidermal growth factor 2; (F)ISH, (fluorescence) in situ hybridization; IHC, immunohistochemistry; ER, estrogen receptor; PR, progesterone receptor; LBA, ligand binding assay; MEK, mitogen-activated protein kinase; EGFR, epidermal growth factor receptor; (RT-)PCR, (reverse transcription-) polymerase chain reaction; GIST, gastrointestinal stromal tumor; PML, promyelocytic leukemia gene; RARA, retinoic acid receptor-alpha; NSCLC, non-small cell lung cancer; ALK, anaplastic lymphoma kinase; EML4, echinoderm microtubule-associated protein-like 4; ERK, extracellular-signal-regulated kinases.
Research to Clinical Utility and FDA approval

- Development of Targeted Therapies based on Molecular Markers
  - Predominance of current research is focused on the identification of actionable molecular markers and development of targeted therapies
  - FDA Approvals of Oncology Pharmaceuticals
    - 2016 – 22 new drugs or indications approved – all targeted agents
    - 2017 (Jan-April) - 8 new or expanded approvals – all targeted agents
    - FDA approving procedures to detect mutations in specific genes for which a targeted therapy is indicated
      - Example – 2017 approved JAK2 RGQ PCR Kit – which will detect mutations in JAK2 gene implicated in Polycythemia Vera

- Somatic Tumor testing approaches – technology will continue to expand
  - Cautionary Approach to ctDNA Assays
  - Research is still evolving regarding the utility of ctDNA assays
  - National guidelines do not currently address as standard of care
  - Patient confusion over germline versus somatic tumor testing
  - Somatic tumor testing can identify potential germline mutations

https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm
Nursing Role in Hereditary Cancer Syndromes

- Oncology Nursing Society Position Statement – revised 2013
  - Oncology Nursing: The Application of Cancer Genetics and Genomics Throughout the Oncology Care Continuum
- Knowledge of the Inherited Cancer Syndromes
  - Features suggesting cancer syndrome –
    - early age of onset,
    - multiple family members affected by similar cancers
    - recognize patterns of cancers that might indicate syndrome
    - obtain a detailed family history for your young patients with cancer
  - Recommend to patients and family to seek a Genetics Counseling evaluation to determine if testing is appropriate
- Knowledge of Nursing role in Cancer Genetics and Genomics
  - Understand the difference between Genetic and Genomic testing procedures
  - Assist patients in understanding the type of testing performed
  - Understand the genetic basis for targeted therapies
  - Recognize that somatic testing does not mean germline testing
ONS and ISONG Genetics Education Initiatives

♦ ISONG and ANA
  • Essential Nursing Competencies and Curricula Guidelines for Genetics and Genomics (2005)
  • Essential Genetic and Genomic Competencies for Oncology Nurses (2012)
  • Professional Credentialing for Advanced Practice Nurse in Genetics – portfolio application relaunched December 2014

♦ ONS
  • Genetic Short Course – Train the Trainer educational program (2000)
  • “Cancer Biology” and “Cancer Genetics” – online courses
  • Cancer Genetic feature article in each edition of Oncology Nursing Forum and Clinical Journal of Oncology Nursing
  • Cancer Genetics Special Interest Group – content experts for defining scope of practice and standards of care for cancer genetics nursing
"You don’t look anything like the long haired, skinny kid I married 25 years ago. I need a DNA sample to make sure it’s still you."