Genomic and Precision Medicine

Week 7: Clinical application of genomics – cancer management

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UCSF Medical Genetics
What’s so special about cancer?

- Second leading cause of death
  - Incidence decreasing
  - 1 in 3 affected
  - Mortality ~50%
- Accessible tissue
- Cancer is a genetic disease

What happens in personalized medicine usually happens in cancer first
Lecture overview

- Cancer biology
- Hereditary cancers
- Tumor genetics
- Clinical applications
Normal cellular proliferation and cancer

Cell division (mitosis) is regulated by cell-cycle controllers, growth factors and their receptors that induce or inhibit proliferation.

Cancer cells have acquired ability to bypass growth signalling and lose growth control.

Cancer invades and metastasizes.

Growth factor
receptor
Growth inhibitors
Cancerous cell
Cancer is a genetic disease

- Loss of growth control is acquired through mutations in the DNA
- Mutations are acquired through faulty DNA damage repair or during normal replication

Exposure to carcinogens

DNA replication errors
What kinds of mutated genes are involved in cancer?

- Oncogenes
- DNA repair enzymes
- Tumor suppressors
- Chromatin modifiers
Proto-oncogenes

- Normally involved in cell cycle and growth signalling
- ‘On’ switch
- When mutated become ONCOGENES
- Gain of function
- Promote proliferation
Known oncogenes disrupting growth signaling in cancer

- Growth factors and receptors
- Intracellular transducers, receptors
- Transcription factors

DNA repair

- DNA repair
DNA repair during replication and exposure to carcinogens

- Excision repair
- Recombinational repair
- Mismatch repair

Image of DNA ligase repairing broken strand of DNA: Courtesy of Tom Ellenberger, Washington University School of Medicine
Tumor suppressors

- Slow cell growth
- ‘Off’ switch
- Signal apoptosis of damaged cells
- Mutated – loss of function

DNA damage → Apoptosis → Macrophage

Growth factor receptor

Growth inhibitors
Cancer genomes are characterized by:

- Mutations in epigenetic machinery
- Global hypomethylation
- Promoter-specific hypermethylation
Model of carcinogenesis

- Proposed by Fearson and Vogelstein in 1990 – colorectal cancer
- Multi-stage process – up to 12 or more independent mutational events ("driver mutations") depending on tumor type
- Cascade effect
- Multi-year process – cancer usually develops over decades
Tumor heterogeneity

- Rapid genetic diversification and selective pressures

Oncogenes and tumor suppressor genes are mutated in cancers. Which is characterized by ‘loss of function’ and which by ‘gain of function’?
Oncogenic mutations are ‘gain of function’ and tumor suppressor mutations are ‘loss of function’
Hereditary cancer
Hereditary vs acquired changes

- Cancer is always a genetic disease
  - Somatic mutations acquired

- Cancer mutations are sometimes inherited
  - Germline
Heritability of cancers

Familial Recurrence Risk

FRR (total) from Utah families

FRR (sibling) from Swedish families

Testicular cancer

Risk to sibling of affected individual is 8-9 times higher than risk in the general population

Risch N. Cancer Epidemiol Biomarkers Prev July 2001 10; 733
Minimum elements for adequate family history of cancer

- Taken at diagnosis and updated regularly
- 1st and 2nd degree relatives
- Ask the following questions about each member of the family who has cancer:
  - Type of primary cancer
  - Age at diagnosis of primary
  - Lineage (maternal or paternal)
  - Ethnicity
  - Results of any genetic testing
Features of hereditary cancers

- In the individual patient:
  - Multiple primary tumors in the same organ or different organs
  - Bilateral primary tumors in paired organs or multifocality within a single
  - Younger-than-usual age at tumor diagnosis
  - Tumors with rare histology
  - Tumors occurring in the sex not usually affected

- In the patient’s family:
  - First-degree relatives with same tumor history
First degree family history increases risk 2-fold

Only 5-10% of breast cancer is hereditary

Inheritance is complex at the disease level, but some individual genes behave in Mendelian fashion

BRCA1/2 – Hereditary Breast and Ovarian Cancer
Genetic basis of hereditary colon cancer

- Family history increases risk 2-4 fold

- Familial adenomatous polyposis (FAP)
  - Mutations in APC gene

- HNPCC – Lynch Syndrome
  - Mutations in DNA repair enzyme genes MLH1, MSH2, MSH6, PMS1, or PMS2
  - accounts for 2%–5% of the total burden of colorectal cancer
Knudson’s 2 Hit hypothesis for tumor suppressor genes

- Tumor suppressors are recessive at cellular level
- Inherited cancers behave as dominant trait

Sporadic cancer
- 2 acquired mutations

Inherited cancer
- 1 inherited and 1 acquired mutation

Time
### Familial cancer syndromes

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Syndrome</th>
<th>Associated Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemias and lymphomas</td>
<td>Ataxia telangiectasia</td>
<td>ATM</td>
</tr>
<tr>
<td>All cancers</td>
<td>Bloom syndrome</td>
<td>BLM</td>
</tr>
<tr>
<td>Breast, ovarian, pancreatic, and prostate cancers</td>
<td>Breast-ovarian cancer syndrome</td>
<td>BRCA1, BRCA2</td>
</tr>
<tr>
<td>Breast, thyroid and endometrial cancers</td>
<td>Cowden syndrome</td>
<td>PTEN</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>Familial adenomatous polyposis (FAP)</td>
<td>APC</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Familial atypical multiple mole-melanoma syndrome (FAMM)</td>
<td>CDKN2A</td>
</tr>
<tr>
<td>Retinal cancer</td>
<td>Familial retinoblastoma</td>
<td>RB1</td>
</tr>
<tr>
<td>Leukemia</td>
<td>Fanconi’s anemia</td>
<td>FACC, FACA</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>Hereditary nonpolyposis colorectal cancer/Lynch syndrome</td>
<td>MLH1, MSH2, MSH6, PMS2</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>Hereditary pancreatitis/familial pancreatitis</td>
<td>PRSS1, SPINK1</td>
</tr>
<tr>
<td>Leukemias, breast, brain and soft tissue cancers</td>
<td>Li-Fraumeni</td>
<td>TP53</td>
</tr>
<tr>
<td>Pancreatic cancers, pituitary adenomas, benign skin and fat tumors</td>
<td>Multiple endocrine neoplasia 1</td>
<td>MEN1</td>
</tr>
<tr>
<td>Thyroid cancer, pheochromacytoma</td>
<td>Multiple endocrine neoplasia 2</td>
<td>RET, NTRK1</td>
</tr>
<tr>
<td>Pancreatic, liver, lung, breast, ovarian, uterine and testicular cancers</td>
<td>Peutz–Jeghers syndrome</td>
<td>STK11/LKB1</td>
</tr>
<tr>
<td>Tumors of the spinal cord, cerebellum, retina, adrenals, kidneys</td>
<td>von Hippel-Lindau syndrome</td>
<td>VHL</td>
</tr>
<tr>
<td>Kidney cancer</td>
<td>Wilms’ tumor</td>
<td>WT1</td>
</tr>
<tr>
<td>Skin cancer</td>
<td>Xeroderma pigmentosum</td>
<td>XPD, XPB, XPA</td>
</tr>
</tbody>
</table>
Li Fraumeni pedigree

Li
Fraumeni
pedigree
When to seek genetic counseling

**Table 2. Cancers for Which Genetic Counseling and Testing Should Be Considered, Even in Absence of Family History**

<table>
<thead>
<tr>
<th>Tumor Diagnosis</th>
<th>Genetic Loci</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common adult cancers</td>
<td></td>
</tr>
<tr>
<td>Triple-negative (ER/PR/HER2-negative) breast cancer, particularly if diagnosed at age &lt; 60 years</td>
<td>BRCA1/BRCA2</td>
</tr>
<tr>
<td>Epithelial ovarian, fallopian tube, or primary peritoneal cancer (most commonly, high-grade serous histology)</td>
<td>BRCA1/BRCA2</td>
</tr>
<tr>
<td>Colorectal cancer demonstrating mismatch repair deficiency (via tumor studies including microsatellite instability analysis and/or immunohistochemistry, excluding known somatic causes including hypermethylation of MLH1 promoter and somatic BRAF mutation)</td>
<td>MLH1/MSH2/MSH3/PMS2/EPCAM</td>
</tr>
<tr>
<td>Endometrial cancer demonstrating mismatch repair deficiency (via tumor studies including microsatellite instability analysis and/or immunohistochemistry, excluding known somatic causes including hypermethylation of MLH1 promoter)</td>
<td>MLH1/MSH2/MSH6/PMS2</td>
</tr>
<tr>
<td>Rare tumors</td>
<td></td>
</tr>
<tr>
<td>Adrenocortical carcinoma, choroid plexus carcinoma</td>
<td>TP53</td>
</tr>
<tr>
<td>Pheochromocytoma, paraganglioma</td>
<td>VHL, RET, multiple SDH loci</td>
</tr>
<tr>
<td>Retinal or cerebellar hemangioblastoma, endolymphatic sac tumor</td>
<td>VHL</td>
</tr>
<tr>
<td>Medullary thyroid cancer</td>
<td>RET</td>
</tr>
<tr>
<td>Pediatric cancers</td>
<td></td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>RB1</td>
</tr>
<tr>
<td>Optic pathway tumor, malignant peripheral nerve sheath tumor, juvenile myelomonocytic leukemia</td>
<td>NF1</td>
</tr>
<tr>
<td>Atypical teratoid/riboblastic tumor</td>
<td>INI1/SMARCB1</td>
</tr>
<tr>
<td>Acoustic or vestibular schwannomas</td>
<td>NF2</td>
</tr>
<tr>
<td>Pulmonary pleuroblastoma</td>
<td>DICER1</td>
</tr>
<tr>
<td>Multiple gastrointestinal polyps</td>
<td>BMPR1A, SMAD4, EPCAM, MLH1, MSH2, MSH6, PMS2, PTEN, APC, STK11, MYH</td>
</tr>
</tbody>
</table>

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

*The cancer types included here are examples of those more commonly encountered by the oncology provider. This list is not intended to be exhaustive and should not be interpreted as guidance to limit the consideration of additional counseling or testing to only those identified. Furthermore, as an increasing number of genes become discovered, this list is likely to change with time.*
Should my patient undergo genetic testing?

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene</th>
<th>Models/Criteria</th>
</tr>
</thead>
</table>
| Lynch syndrome                | MLH1, MSH2, MSH6 | PREMM model: http://premm.dfci.harvard.edu  
                               |             | MMRPRO model: http://bcb.dfci.harvard.edu/bayesmendel/mmrproqa.html |
| Breast and ovarian cancer     | BRCA1, BRCA2 | BRCAPRO model: http://bcb.dfci.harvard.edu/bayesmendel/bracapro.php  
                               |             | PENN2 model: http://www.aflri.upenn.edu/tacc/penn2  
                               |             | MYRIAD risk calculator and prevalence tables: http://www.myriadtests.com/provider/brca-mutation-prevalence.htm  
                               |             | BOADICEA Cambridge University Web site: http://ccge.medschl.cam.ac.uk/boadicea/web-application/ |
| Melanoma                      | CDKN2A (p16) | MELAPRO model: http://bcb.dfci.harvard.edu/bayesmendel/melapro.php  
                               |             | PANCPRO model: http://bcb.dfci.harvard.edu/bayesmendel/pancpro.php |
| Pancreatic cancer             | TP53       | CHOMPRET criteria: http://jco.ascopubs.org/content/27/26/e108.full.pdf |
| Li-Fraumeni syndrome          |            | PTEN risk model: http://www.lerner.ccf.org/gmi/ccscore/ |
| Cowden syndrome               | PTEN       |                                                                 |

# Resources for locating cancer genetics specialists

<table>
<thead>
<tr>
<th>Resource</th>
<th>Web Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>American College of Medical Genetics Provider Directory</td>
<td><a href="http://www.acmg.net/GIS/Disclaimer.aspx">http://www.acmg.net/GIS/Disclaimer.aspx</a></td>
</tr>
<tr>
<td>American Board of Medical Genetics</td>
<td><a href="http://www.abmg.org/pages/searchmem.shtml">http://www.abmg.org/pages/searchmem.shtml</a></td>
</tr>
<tr>
<td>American Board of Genetic Counselors</td>
<td><a href="https://abgcmember.goamp.com/Net/ABGCWcm/Find_Counselor/ABGCWcm/PublicDir.aspx?hkey=0ad511c0-d9e9-4714-bd4b-0d73a59ee175">https://abgcmember.goamp.com/Net/ABGCWcm/Find_Counselor/ABGCWcm/PublicDir.aspx?hkey=0ad511c0-d9e9-4714-bd4b-0d73a59ee175</a></td>
</tr>
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</table>
Genetic testing for known cancer susceptibility genes

- A negative test result is no guarantee that cancer WILL NOT develop
- A positive test result is no guarantee that cancer WILL develop
- Risk management strategies for a positive test (e.g. BRCA1 – breast cancer)
  - Surveillance
  - Hormone therapy
  - Lifestyle changes
  - Prophylactic surgery
Cancer is primarily due to which type of mutations, somatic or germline?
Cancer is always a somatic disease; only 5-10% of cancers are inherited.
Tumor genetic landscape
Measuring tumor gene expression

- One or a few genes at a time: e.g. HER2, ER, PR
- Genome-wide measures (Expression microarrays, RNA-seq)

**Expression Microarrays**
- Fixed probes
- Different features (e.g. bind different genes)
  - Fully complementary strands bind strongly
  - Partially complementary strands bind weakly

**RNA-sequencing**
- Labelled copies of tumor RNA
Measuring somatic mutations in tumors

- Sequencing DNA from tumor-normal pairs

- Tumor DNA

- Normal DNA

- Germline variants and somatic changes

- Germline variants
Large-scale efforts to characterize tumors at the molecular level

http://cancergenome.nih.gov/

International Cancer Genome Consortium
How many genes are mutated in the average solid tumor?

33-66 genes in an average solid tumor
Mostly SNVs
Variable by cancer type
Why?
Drivers and passengers

- Driver mutations provide a selective growth advantage
- Passenger mutations have no effect on neoplastic growth
- How to identify driver genes?
  - Mountains and hills (frequency)
  - Patterns

Wood LD. Science 2007: 318 (5853);1108-1113
Distribution of mutations and mutation types across IDH1 in brain tumors

http://gdac.broadinstitute.org/runs/analyses__2013_01_16/reports/cancer/SKCM-TM/mutsignozzlereports2n/nozzle.html
How many driver genes exist?

- 3284 tumors sequenced
- 294,881 mutations reported
- 125 mutation driver genes identified
  - 71 tumor suppressor genes
  - 54 oncogenes

Basis of metastatic disease

- Specific mutated genes that lead to metastasis?
- Stochastic process more likely
- Metastatic disease accounts for >90 percent of cancer deaths

Images courtesy of US National Cancer Institute
Clinical applications: prognosis and treatment response
Histological classification of breast cancer

Histological classification
Infiltrating Ductal
Infiltrating Lobular
Other
Mixed
Mucinous
Medullary

- Morphology-based
- Similar morphology can exhibit different clinical presentations, disease aggressiveness and treatment responsiveness
Immunohistochemical classification

Most common
Most favorable
Diagnosed later
Usually ductal

Don’t predict node status or metastasis

Breast cancer prognostic markers

- **Oncotype DX**® (Genomic Health)
  - A 21-gene expression score (16 prognostic genes and 5 housekeeping)
  - Scale of 0-100, strata of low, intermediate or high risk
  - Predicts 10-year risk of distant recurrence in Estrogen Receptor (ER) positive breast cancers (may benefit from adding chemo to their hormone treatment)
  - Predicts responsiveness to CMF (Cyclophosphamide, Methotrexate and 5-Fluorouracil) chemotherapy

- **MammaPrint**® (Avendia)
  - A 70-gene expression profile
  - Regardless of estrogen receptor (ER) status, with tumors of less than 5 cm
  - Distinguishes those predicted to have good prognosis (no relapse within 5 years) from poor prognosis (relapse within 5 years)
HER2-positive breast cancer

- The HER2 gene is amplified in 20% of breast cancers
- Referred to as HER2-positive cancers
- Make more HER2 protein than HER2-negative cancers

The extra HER2 protein causes increased signal pathway activation, which contributes to the uncontrolled growth and survival of these cancers.
HER2- Herceptin

Herceptin® (trastuzumab) is a monoclonal antibody that binds to HER2. This prevents the receptor from activating the pathways that promote the proliferation and survival of breast cancer cells.
Chronic myelogenous leukemia (CML)

Blood cancer caused by reciprocal translocation (Philadelphia Chromosome), resulting in oncogenic BCR-ABL gene fusion

BCR-ABL found in 95% of CML

Multiple targeted medications have been created which specifically inhibit this oncogene (imatinib, dasatinib, nilotinib)

Previously – median survival 4 years

Survival now 20-25 years
KRAS mutations in colorectal cancer

Normal EGF + KRAS Growth Control

Mutated KRAS Causes Unchecked Growth

EFG-targed Drugs Block Growth Signals

Anti-EGFR therapies (anti-EGFR therapies cetuximab (Erbitux) and panitumumab (Vectibix) don’t work in KRAS-mutated cancers
Vemurafenib and malignant melanoma

**Normal**

- RAS
- BRAF
- MEK
- ERK

**Mutant BRAF (~50% of melanomas)**

- RAS
- BRAF V600
- MEK
- ERK

BRAF inhibitors (Vemurafenib) block constitutive activation of downstream pathway to decrease cellular proliferation.
Lung cancer – histological classification

Lung Cancer

- Small cell (20%)
  - Classical
  - Large Cell Neuroendocrine
  - Combined

- NSCLC
  - Adenocarcinoma
  - Squamous Cell Carcinoma
  - Large Cell Carcinoma
  - Bronchoalveolar Carcinoma
Lung cancer molecular classification and targeted therapy

- Lung Cancer
  - Small cell (20%)
    - KRAS
    - EGFR
      - Erlotinib
      - Gefitinib
  - NSCLC
    - ALK
      - Crizotinib
      - Others in development
    - Other
    - Unknown
    - Other
    - Unknown
Different cancers may share common genetic alterations

**BRAF**

60% of melanomas
Respond to the BRAF inhibitor vemurafenib

100% of hairy cell (HC) leukemias
Response to BRAF inhibitor

5-10% colorectal cancers
No response to BRAF inhibitor

Tumor profiling in the clinic

- Many academic medical centers beginning to offer testing
- Commercial options
  - FoundationOne
  - Caris Target Now
  - SNaPshot
- Only activated oncogenes are targetable; tumor suppressor genes (loss of function) are not
- Most useful – link to treatment OR clinical trials

Find a Cancer Mutation

Find Clinical Trials

Vanderbilt-Ingram Cancer Center
Challenges in Molecular Profiling for Targeted Treatment

- Bioinformatics

- What does it mean when a mutation normally associated with an inherited cancer is found in a tumor sample?

- Tumor heterogeneity

- Tumor targets identified but therapy not approved or reimbursed for that indication
Advances in cancer genomics

- Continued development of targeted treatments
- New treatment paradigms – immunotherapy
- Improved diagnosis - liquid biopsies