Pathology and the Third Wave of Medical Genomics

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Conflict of Interest Disclosure
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Medical Genomics: The Third Wave
The Human Genome will yield many new drugs
GWAS data will help us manage common diseases
Precision diagnostics will lead to better outcomes

Steve Jobs’ Cancer Timeline*
*Based on Steve Jobs: A Biography by Walter Isaacson (Simon & Schuster, New York, 2011)

It’s 2013 and I have cancer – what do I do?

I’ve heard that having my tumor DNA analyzed may tell me why my cancer is different and what my doctor can do about it.

On the internet I learned that it only costs $1,000 to analyze my genome.
Definitions

What is a human genome?
- A "whole genome" consists of ~3 gigabytes (3 billion "base pairs") of DNA distributed unequally among 22 autosomes & 1 sex chromosome (haploid genome).
- Approximately 98% of the this DNA is "intergenic" (literally "between genes"), does not encode proteins and is of unknown medical relevance.

What is a human exome?
- Exome refers to the 2% subset of the whole genome that encompasses our ~23,000 pairs of genes.
- Because each gene, on average, is composed of 8 protein-encoding segments ("exons"), an exome corresponds to 8 × 23,000 = 184,000 segments of DNA.

What is a human transcriptome (a.k.a. gene expression profile)?
- Transcriptome refers collectively to all of the "expressed" RNA "transcripts" of genes based on the "central dogma" of molecular biology, i.e. DNA → RNA → protein.
- A transcriptome reflects what a cell is doing at a particular point in time (molecular phenotype) as opposed to what it is capable of doing (genotype).

Categories of Clinical Genomics

**Presymptomatic (prospective) genotyping for disease risk assessment**
- Examples
  - Newborn screening*
  - Carrier testing
  - GWAS

**Post-diagnostic genotyping for targeted therapy, treatment optimization**
- Examples
  - Tumor "subtyping"
  - Pharmacogenomics

*Newborn Genome Screening: "Bright Futures" or "Gattaca?"

MedPage Today 9/38/2012

New Paradigm for the Laboratory Diagnosis of Cancer

Case History #1

78 y/o male, no prior H/D Cancer
Presented with throat discomfort;
Biopsy revealed papillary adenocarcinoma
Underwent laser resection & lymph node dissection, 3/21 nodes positive;
60 Gy adjuvant radiation therapy
4 months later, PET-CT showed numerous small bilateral pulmonary metastases; IHC of biopsy showed
2+ EGFR
On basis of IHC, pt. started on an EGFR inhibitor, lack of response & tumor progression
First diagnostic whole genome & transcriptome analysis performed

Process of Molecular Diagnosis for Personalized Therapy

- **Genome Sequencing & Analysis**: Compare tumor genome with somatic genome and look for potential "driver" mutations.
- **Transcriptome Analysis**: Gene expression profile of tumor to look for overexpressed drug targets.
- **Search of pharmacopoeia**: Relate mutations and gene expression data to drugs with known therapeutic targets and mechanisms of action.

Clinical Course

In cancer, tumor genome analysis will be done not once, but multiple times during the course of the disease for tumor subtyping, monitoring response to therapy and diagnosing the reasons for recurrences or therapeutic failures.

"Pathology Report"

Patient was switched from an EGFR inhibitor to a RET inhibitor.

You Have To Know Someone

Christopher Hitchens

Francis Collins, M.D., Ph.D.

http://www.medpagetoday.com/Blogs/CelebrityDiagnosis/25732
"The process of making molecular data rapidly available to treating physicians is a major logistical hurdle that must be overcome."

"Cancer will increasingly be seen as a disease defined primarily by its genetic fingerprint rather than just by the organ where it originated."

NY Times May 2, 2013

30% of Genetic Tests are Misordered

Doctors’ Mistakes in Genetic Test Orders Is Warning Signal to Pathologists and Clinical Laboratories

There is an unsustainable proliferation of “genetic” tests

Workforces for Personalized Genomic Medicine
Tumor DNA analysis can be a universal companion diagnostic for targeted therapies. It’s also important to assess eligibility for clinical trials.

Genome analysis is not just for cancer

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<thead>
<tr>
<th>Specialty Area</th>
<th>Treating Institution</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Nephrology</td>
<td>Yale University Hospital</td>
<td>Choi et al., 2009</td>
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<td>Neurology</td>
<td>Baylor College of Medicine</td>
<td>Lupski et al., 2010</td>
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<tr>
<td>Oncology</td>
<td>Vancouver General Hospital, Canada</td>
<td>Jensen et al., 2010</td>
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<tr>
<td>Gastroenterology*</td>
<td>Medical College of Wisconsin</td>
<td>Worthey et al., 2011</td>
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<td>Oncology</td>
<td>Washington University, St. Louis</td>
<td>Welch et al., 2011</td>
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<td>Bainbridge et al., 2011</td>
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Recommended Reading and Viewing

- Customized Care 2020: Medical Genomics, Network Biology & Personalized Medicine
  - [http://prime.com/prime-reports/b/1/73](http://prime.com/prime-reports/b/1/73)
- Pathologists and the third wave of medical genomics
- Personal Genotypes are Teachable Moments
  - [http://www.markboguski.net/docs/publications/gm426.pdf](http://www.markboguski.net/docs/publications/gm426.pdf)
- The Idolatry of the $1,000 Genome
  - [http://vimeo.com/38578986](http://vimeo.com/38578986)
- IBM Watson: Fighting the Last War

Personal Medical Genomes: Where celebrities go, the public often follows

- Sergey Brin
- Glenn Close
- Ozzy Osbourne

[http://www.medpagetoday.com/CelebrityDiagnosis/34963](http://www.medpagetoday.com/CelebrityDiagnosis/34963)
Acknowledgements