When Precision Medicine Is Not So Precise

Neil Spector, MD
Associate Professor of Medicine and Pharmacology/Cancer Biology
Sandra Coates Chair in Breast Cancer Research
Director, Developmental Therapeutics Program
Duke Cancer Institute
Duke University School of Medicine
“Medicine is a science of uncertainty and an art of probability.”

William Osler (1849-1911)
What is the diagnosis?

- Fever (mild, continuous, spiking)
- Malaise
- Weight loss
- Anemia
- Lymph adenopathy (regional or generalized)
- Non pruritic rash
- Alopecia
- Eye (keratitis, iritis)
- Esophagitis
- Proteinuria (occasionally nephrotic syndrome)
- Arthritis
- Neuropathy
- Dementia

Systemic Signs and Symptoms of the Great Masquerader: Syphilis
Behavior/Lifestyle/Travel History

Physical Exam

“Omics”

Family History
How do you paint a portrait in the current environment?

• Average physician visit in the U.S. is 15-18 minutes start to finish

• One study from the U. South Carolina found that patients were interrupted by their clinician after only 12 seconds
Payment = [(RVU work x GPCI work) + (RVU PE x GPCI PE) + (RVU malpractice x GPCI malpractice)] x Conversion Factor
Precision Medicine is an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment and lifestyle for each person.

NIH website
Precision Cancer Care in 2017

Blood

DNA

RNA

PROTEIN

Tumor

Genomics

gene amplification/deletion
rearrangements, mutations

Epigenomics

DNA methylation,
histone modifications

Gene expression

mRNA, miRNA

Proteomic

Metabolomics

Best therapeutic option

Patient

Pharmacogenomics

Statistomics

Cancer Treatment Strategy (pre-1990s)
Emerging and Enabling Characteristics of Cancer

Emerging Hallmarks
- Deregulating cellular energetics
- Avoiding immune destruction

Enabling Characteristics
- Genome instability and mutation
- Tumor-promoting Inflammation

Hanahan and Weinberg Cell 144: 646 (2011)
<table>
<thead>
<tr>
<th>Targeted Drugs</th>
<th>Target(s)</th>
<th>FDA-approved indication(s)</th>
<th>Annotations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ado-trastuzumab\ explanatory text</td>
<td>HER2 (ERBB2/neu)</td>
<td>Breast cancer (HER2+)</td>
<td>Detection of HER2 by immunohistochemistry (IHC) methods</td>
</tr>
<tr>
<td>Afatinib (Gilotrif)</td>
<td>EGFR (HER1/ERBB1), HER2 (ERBB2/neu)</td>
<td>Non-small cell lung cancer (with EGFR exon 19 deletions or exon 21 substitution (L858R) mutations)</td>
<td></td>
</tr>
<tr>
<td>Aldeleukin (Proleukin)</td>
<td>IL2 Receptor</td>
<td>Renal cell carcinoma</td>
<td></td>
</tr>
<tr>
<td>Axitinib (Inlyxa)</td>
<td>KIT, PDGFRβ, VEGFR1/2/3</td>
<td>Renal cell carcinoma</td>
<td></td>
</tr>
<tr>
<td>Belinostat (Beleodaq)</td>
<td>HDAC</td>
<td>Peripheral T-cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>Bevacizumab (Avastin)</td>
<td>VEGF ligand</td>
<td>Cervical cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Colorectal cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fallopian tube cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Glioblastoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-small cell lung cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ovarian cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peritoneal cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal cell carcinoma</td>
<td></td>
</tr>
<tr>
<td>Bortezomib (Velcade)</td>
<td>Proteasome</td>
<td>Multiple myeloma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mantle cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>Bosutinib (Bosulif)</td>
<td>ABL</td>
<td>Chronic myelogenous leukemia</td>
<td>Monitor acquired mutation of ABL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Philadelphia chromosome positive)</td>
<td></td>
</tr>
<tr>
<td>Brentuximab vedotin (Ad cetris)</td>
<td>CD30</td>
<td>Hodgkin lymphoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anaplastic large cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>Cabozantinib (Cometriq)</td>
<td>FLT3, KIT, MET, RET, VEGFR2</td>
<td>Medullary thyroid cancer</td>
<td></td>
</tr>
<tr>
<td>Canakinumab (Ilaris)</td>
<td>IL-1β</td>
<td>Juvenile idiopathic arthritis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cryopyrin-associated periodic syndromes</td>
<td></td>
</tr>
<tr>
<td>Carfilzomib (Kyprolis)</td>
<td>Proteasome</td>
<td>Multiple myeloma</td>
<td></td>
</tr>
<tr>
<td>Ceritinib (Zykadia)</td>
<td>ALK</td>
<td>Non-small cell lung cancer (with ALK fusion)</td>
<td></td>
</tr>
<tr>
<td>Cetuximab (Erbitux)</td>
<td>EGFR (HER1/ERBB1)</td>
<td>Colorectal cancer (KRAS wild type)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Squamous cell cancer of the head and neck</td>
<td></td>
</tr>
<tr>
<td>Crizotinib (Xalkori)</td>
<td>ALK, MET</td>
<td>Non-small cell lung cancer (with ALK fusion)</td>
<td></td>
</tr>
<tr>
<td>Dabrafenib (Tafinlar)</td>
<td>BRAF</td>
<td>Melanoma (with BRAF V600 mutation)</td>
<td></td>
</tr>
<tr>
<td>Dasatinib (Sprycel)</td>
<td>ABL</td>
<td>CML t(9;22) positive</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acute lymphoblastic leukemia (ALL)</td>
<td>Monitor acquired mutation of ABL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>t(9;22) positive</td>
<td></td>
</tr>
<tr>
<td>Denosumab (Xgeva)</td>
<td>RANKL</td>
<td>Giant cell tumor of the bone</td>
<td></td>
</tr>
<tr>
<td>Erlotinib (Tarceva)</td>
<td>EGFR (HER1/ERBB1)</td>
<td>Non-small cell lung cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pancreatic cancer</td>
<td></td>
</tr>
<tr>
<td>Everolimus (Afinitor) mTOR</td>
<td></td>
<td>Pancreatic neuroendocrine tumor</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal cell carcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nonresectable subependymal giant cell astrocytoma associated with tuberous sclerosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Breast cancer (HR+, HER2-)</td>
<td></td>
</tr>
<tr>
<td>Gefitinib (Iressa)</td>
<td>EGFR (HER1/ERBB1)</td>
<td>Non-small cell lung cancer with known prior benefit from gefitinib (limited approval)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-Hodgkin’s lymphoma</td>
<td></td>
</tr>
<tr>
<td>Ibritumomab tiuxetan (Zevalin)</td>
<td>CD20</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Director, Translational Oncology Research (1998-2006)
The Molecular Biology of Cancer Cells

Hanahan and Weinberg Cell 100:57–70 (2000)
Pre-treatment

On therapy
Successful History of Translational Research

- **ER mediated resistance:** Xia et al. “A model of acquired autoresistance to ErbB2 tyrosine kinase inhibitors and a therapeutic strategy to prevent its onset in breast cancer.” *Proc. Natl. Acad. Sci. USA* 2006; 103: 7795-7800. Led to FDA approval of letrozole + lapatinib (1st line HER2+/ER+ MBC)


“You will be dead by Monday without a transplant.”

Heart Transplant Surgeon (UNC)
Friday, July 17, 2009
Evolution of a Disaster

I was 37 years old.

• Previously very active and healthy (Boston Marathon x 2)
• No significant family history (cardiac, neurological, endocrine, psychiatric, rheumatologic)
• No medications. No substance abuse. Never smoked.
• Barely missed a day of work in my professional life
Initial Symptoms (1993)

• Multiple ER visits for palpitations starting within six months of moving to Miami
• Admitted for MI-like chest pain (negative cardiac w/u)
• Episode “brain fog” (like taking Benadryl 50 mg every two hours): lasted a few weeks and lifted
  – Gave a 60 minute lecture on my research and had no recollection of what I had talked about afterwards.
• Extreme fatigue (went from running 60 miles a week to not being able to walk 10 yards without stopping to rest)
Symptoms (1993-1997)

- Difficulty concentrating
- Dysesthesia (“burning sensation”) on my feet
- Constant cardiac arrhythmias
  - Late 1996/early 1997 documented second degree heart block (Wenckebach)
- Diffuse myalgia
- Severe sleep disturbance (insomnia)
Work Up

Extensive laboratory work up including rheumatologic panels

• Elevated total IgM antibody (2x normal)
• *Increased anticardiolipin antibody (IgM) titer including ESR – Otherwise all labs are normal CBC, chemistries, LFTs
• Stress MUGA, multiple Holter Monitor tests
• Abnormal Tilt Test

DIAGNOSIS: NEUROGENIC SYNCOPE
DIAGNOSIS: STRESS
Spring 1997

- Develops frank arthritis (erythema, swelling, tenderness)
- Rapidly resolves with course of doxycycline being administered for another reason
- Conclusion: Non-specific anti-inflammatory effects of tetracycline class of antibiotics

June 1997

**Chief Complaints:** fatigue; palpitations; waking up in the middle of the night with exploding headache and flash of white light

**Findings:**

- Complete heart block with runs of non-sustained ventricular tachycardia and six second pauses (Holter Monitor)
- Weight loss (15-20 pounds)
Work Up

- Lyme disease serology (at the request of the patient)
- First test: Very high anti-Lyme IgM titer secondary Western blot analysis inconclusive

**DIAGNOSIS:** IDIOPATHIC CARDIAC CONDUCTION DEFECT

**TREATMENT:** INSERTION OF DUAL CHAMBER PACEMAKER/DEFIBRILLATOR
“Denial is the most common reaction of someone your age when confronted with heart disease.”

(World Renowned Academic Cardiologist)
August 1998

- Echocardiogram: global dysfunction
- 10% LVEF
House Bill 1933, sponsored by Delegate Barbara Comstock and others, requires the following notification to be given to anyone being tested for Lyme disease.

“ACCORDING TO THE CENTERS FOR DISEASE CONTROL AND PREVENTION, AS OF 2011 LYME DISEASE IS THE SIXTH FASTEST GROWING DISEASE IN THE UNITED STATES. YOUR HEALTH CARE PROVIDER HAS ORDERED A LABORATORY TEST FOR THE PRESENCE OF LYME DISEASE FOR YOU. CURRENT LABORATORY TESTING FOR LYME DISEASE CAN BE PROBLEMATIC AND STANDARD LABORATORY TESTS OFTEN RESULT IN FALSE NEGATIVE AND FALSE POSITIVE RESULTS, AND IF DONE TOO EARLY, YOU MAY NOT HAVE PRODUCED ENOUGH ANTIBODIES TO BE CONSIDERED POSITIVE BECAUSE YOUR IMMUNE RESPONSE REQUIRES TIME TO DEVELOP ANTIBODIES. IF YOU ARE TESTED FOR LYME DISEASE, AND THE RESULTS ARE NEGATIVE, THIS DOES NOT NECESSARILY MEAN YOU DO NOT HAVE LYME DISEASE. IF YOU CONTINUE TO EXPERIENCE SYMPTOMS, YOU SHOULD CONTACT YOUR HEALTH CARE PROVIDER AND INQUIRE ABOUT THE APPROPRIATENESS OF RETESTING OR ADDITIONAL TREATMENT.”
Lyme Disease: The Basics

*Borrelia Burgdorferi*

- Spirochete, cousin to the bacteria which causes syphilis, can invade any body part

**Symptoms**
- Huge spectrum of illness/health
- Asymptomatic infection to severe illness
- Spontaneously waxing and waning
Lyme disease* is a multisystem illness caused by *Borrelia burgdorferi*, a spirochete transmitted by certain species of *Ixodes* ticks. Approximately 30,000 confirmed and probable cases of Lyme disease were reported in the United States in 2012, primarily from high-incidence states in the Northeast (Connecticut, Delaware, Maine, Maryland, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, and Vermont) and upper Midwest (Minnesota and Wisconsin) (1,2).† Common manifestations include cutaneous, neurologic, and rheumatologic signs and symptoms. Symptomatic infection of the heart is rare in recognized Lyme disease cases and usually resolves promptly with appropriate antibiotic therapy. Nonetheless, cardiac involvement occasionally can cause life-threatening cardiac conduction abnormalities. During November 2012–July 2013, one woman and two men (ranging in age from 26 to 38 years) from high-incidence Lyme disease states experienced sudden cardiac death and, on postmortem examination, were found to have evidence of Lyme carditis. The three deaths were investigated by the Connecticut Department of Public Health, Massachusetts Department of Public Health, New Hampshire Department of Public Health, New York State Department of Health, and CDC. Donated corneas from two decedents had been transplanted to three recipients before the diagnosis of Lyme disease was established, but no evidence of disease transmission was found. Although death from Lyme carditis is rare, it should be considered in cases of sudden cardiac death in patients from high-incidence Lyme disease regions.
Dilated Cardiomyopathy and Lyme Disease

- Study of 110 patients in an academic center in the Czech Republic with dilated cardiomyopathy
  - 22 patients (20%) were positive for *Borrelia* b. by PCR from endomyocardial biopsy
  - One of the 22 had 1st degree AV block; LBBB (N=5); RBBB (N=2)
  - Elevated troponin in 38% of the 22 patients testing
  - Only 36% were IgG positive by Western blot (despite symptoms >30 days)
  - None of the patients reported an EM rash or other typical LD symptoms

“The inability of antibiotic treatment to achieve normalization of LV systolic function in all of the *Bb*-positive patients may be explained by the fact that in many affected subjects, longstanding *Bb* infection may have caused irreversible myocardial damage.”

“The good physician treats the disease. The great physician treats the patient who has the disease.”

William Osler
Staying Alive for the Next 11 Years

Taking control of my life
- Lots of exercise (45 minutes on the Nordic Track 6 days/week)
- Stress Reduction (Mind-Body Exercises)
- Not letting cardiomyopathy define my life
- Live life to the fullest
  - Developed two targeted cancer drugs from the bench through FDA approval
  - Coached my daughter’s soccer teams
  - Traveled the world
  - Continued my work helping others
Don’t let life events define who you are or limit what you can do. 

Perseverance!
Re-Prioritize My Life

- Experimental Results
- Manuscript Review
- Grant Review
- Writing what I thought would be my last letter to my 11 year old daughter

Have someone who is strong and rational and can help counteract the doubt and anxiety that inevitably arises.
One Size Fits All Treatment Strategy

Antibiotics (21 days)

Great outcome

WHY and WHAT is the underlying cause(s)??

Chronic problems
1386 annotated genes in the main chromosome and small DNA replicons

Typical genomes - ~10% encodes a purine utilizing enzyme

Potentially – 130 druggable targets
Rapid Lead Generation Engine

ATP Resin → GFP-Protein X → +Fluor → Drug + Resin → Centrifuge Filter → Eluted Protein

Fluorescence Counts

Well Number

1 21 41 61 81

0.0E+00 5.0E+04 1.0E+05 1.5E+05 2.0E+05 2.5E+05
Acknowledgements

• Wenle Xia
• Sumin Zhou
• David Alcorta
• Sarah Sammons (Med Onc fellow)
• Megan Moore (Duke undergrad)
• Tim Haystead (Pharmacology/Cancer Biology)
• Kim Lyerly (Surgery)
Save a life. Become an organ donor.