ACP 2013
(Genetics)
Cost-Effective Genetic Screening for the Internist

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Slides/Questions ➔ matthew.taylor@ucdenver.edu

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The Full Disclosure

Matthew Taylor MD, PhD has disclosed relationships with entities producing, marketing, re-selling, or distributing health care goods or services consumed by, or use on, patients:

- Genzyme Therapeutics Research (Grant)
- Research (Clinical Trial)
- Amicus Therapeutics Research (Clinical Trial)
- Protalix Therapeutics Research (Clinical Trial)
- Synageva Therapeutics Research (Grant)

- Consulting: Array Biopharma, Guidepoint Global, Genomic Health, GlaxoSmithKline
Roadmap

• Genetic Testing
  – "Cost Effectiveness of genetic testing"
  – Evolution of genetic testing
  – Roles of genetic testing
  – Patient impact of genetic testing
Cost-Effective Genetic Screening for the Internist

Costs/Consequences of 2 or more courses of action are evaluated → QALYs

PubMed ‘Cost-effectiveness Analysis’
64,247 articles

‘Testing’ of patient/family/population, for diagnosis/risk assessment

PubMed ‘Genetics’
2,422,243 articles

Internal Medicine ‘327,787’
64,247 articles

above combined = 29 articles (9, English last 5 years)
Utility of a ‘Diagnostic Test’

Perfect Diagnostic Test → Diagnoses Treatable Disease → Patient Outcome(s) Improved

Rapidly moving disease / Highly reversible
Slow moving disease / Somewhat reversible
Genetic Diagnosis / Possibly treatable (some cases)
Genetic Risk / Prevention? Treatment?
Family Risk in your Patient’s relatives / Action? Prevention? Treatment?
Summary: Cost Effectiveness

• **Paucity of data on cost-effectiveness of genetic testing**

• **Genetic diseases**
  – Some untreatable (can’t assess QALYs)
  – Long time between genetic risk (birth) and disease
  – Gene discovery (many) in past 5 years
“Houston, we have a problem...”
It is now possible to....

- Test ~4,000 (20,000) genes in a single assay
- Do genetic testing on a single cell
- Use genomics to confirm a hospital outbreak
- Diagnose Down Syndrome from a blood test
- Test for >200 conditions for $99
- Correct DNA mutations in diseased cells
- Use DNA to confirm ancestry
- Use DNA to identify ‘anonymous’ individuals
- Find King Richard III in a parking lot
Roadmap

- Genetic Testing
  - Cost Effectiveness of genetic testing
  - Evolution of genetic testing
  - Roles of genetic testing
  - Patient impact of genetic testing
Evolution of Diagnostic Tests

Diagnosis → Predictive

When will we move from this? ...to this?
Genetic Testing is Growing

Growth of Laboratory Directory

12/02/2012

571 GeneReviews
1111 Clinics
629 Laboratories testing for
2888 Diseases
2639 Clinical
249 Research

Cost per Genome

October 2001

Moore's Law

July 2011

http://www.nap.edu/catalog.php?record_id=13284
Gene Discovery → Genetic Testing → Prognosis/Prediction → Management

**Heart Diseases**
- Hypertrophic Cardiomyopathy
- Idiopathic Dilated Cardiomyopathy
- Long QT / Sudden Death

**Cancers**
- Hereditary Breast/Ovarian
  - Familial Polyposis
- Lynch/HNPCC (Colon/Endometrial)

**Renal Diseases**
- Polycystic kidney disease
- Familial Hypertensive diseases
  - Fabry disease
  - Alport syndrome

**Lung Diseases**
- Emphysema (alpha-1-antitrypsin)
  - Recurrent pneumothorax
  - Adult onset Cystic Fibrosis
  - Pulmonary Hypertension

**Endocrine Diseases**
- Multiple Endocrine Neoplasias
- Maturity Onset Diabetes of the Young
  - Adrenal leukodystrophy

**Connective Tissue Diseases**
- Marfan syndrome
- Hypermobility / Ehlers Danlos
American Medical Association Survey

- 59% of Americans somewhat or very likely to take advantage of genetic testing

- 72% believe that their primary care physicians can interpret these results
  - Genetic Testing: A study of consumer attitude
  - AMA March 1998

Normal
23andMe can help you manage risk and make informed decisions...

Learn valuable health & ancestry information.

$99

Order Now
23andMe 2012 Top Genetic Discoveries

- **A Genetic Variant Protective Against Alzheimer’s Disease**
  - APP A673T associated with about five times lower odds of Alzheimer’s. (23andMe reports on APOE ‘risk’ and APP ‘protective’ variant status)

- **ENCODE Project Creates an Map of the Uncharted Areas of the Genome**
  - ~400 scientists studying ‘junk DNA’ → not really silent junk after all

- **Noninvasive Prenatal Sequencing**
  - Genome sequencing in fetuses non-invasively (earlier than and without Amniocentesis or Chorionic Villus Sampling)

- **New Insights into Myeloproliferative Disorders**
  - Associations with ATM and TERT genes (done by 23andMe with 1,000 recruited ‘customers’)

- **New Insights into the Human Origins and Evolution**
  - Out of Africa, intermixing with Neanderthals, role of rare genetic variants

- **Family Medical History and Genetics Best Used Together to Predict Disease**
  - 23andMe developed model that genetic tests AND family history more predictive of disease risks

- **Older Dads’ Biological Clocks**
  - Older males (older testicles) → more de novo mutations

- **Breast Size Matters, But Not How You Think**
  - Identified genetic markers influencing breast size and some of same markers also influencing breast cancer

- **New Treatment for Cystic Fibrosis**
  - FDA approved ivacaftor (2012) as new mutation-targeting treatment for Cystic Fibrosis

- **Autism Study Reveals No Genetic Associations**
  - Large study found no SNPs predictive of autism risks (other genetic mechanisms may be at play; currently aCGH + other tests identify genetic cause in ~15-20% of autism)
Striving to look and feel better? Wish you had more energy?

Pathway Fit® will help you take the first step. Click here to connect with a provider today!

Work Smarter, Not Harder with Nutrigenetics
Receive personalized information and recommendations based on your genetics to assist you in achieving your nutritional goals.

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Explore Our DNA Customized Nutritional Supplements Explore Our Customized DNA Skin Care Product Line

dna customized nutritional supplements
300 gel capsules/30 day supply

$129.00 + S&H + Tax Where Applicable

Using a sample you collect to unlock your unique genetic code - we can identify problem genes, and

Customize For Me Now!

For optimum results we recommend a full regimen of geneMe products

Buy customized bundle
Summary: Evolution of Genetic Tests

- Testing availability growing exponentially
- Costs dropping exponentially
- Free-market forces are driving testing into clinics, hospitals, internet, Walmart, iPhones
Inflection Point

Predictive

What is it?
What has happened?

Descriptive
Diagnostics

Quantitative Prediction
What is the risk(s)?
What will happen?

Qualitative

What is it?
• Genetic Testing
  – Cost Effectiveness of genetic testing
  – Evolution of genetic testing
  – Roles of genetic testing
  – Patient impact of genetic testing
CASE: 19 y/o healthy woman

- Exercising: weights → hot tub → swimming
- “Found down” in 4 feet of H2O
- CPR → temporary recovery → died day 12

QTc = 0.60 sec^{1/2}
Long-QT Syndrome

Dan M. Roden, M.D.

Table 2. Guidelines for Management of the Long-QT Syndrome.*

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level of Evidence</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>No participation in competitive sports</td>
<td>I</td>
<td>Includes patients with the diagnosis established by means of genetic testing only</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>I</td>
<td>For patients who have QTc-interval prolongation (&gt;460 msec in women and &gt;440 msec in men)</td>
</tr>
<tr>
<td></td>
<td>IIa</td>
<td>For patients with a normal QTc interval</td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>For survivors of cardiac arrest</td>
</tr>
<tr>
<td></td>
<td>IIa</td>
<td>For patients with syncope while receiving beta-blockers</td>
</tr>
<tr>
<td></td>
<td>IIb</td>
<td>For primary prevention in patients with characteristics that suggest high risk; these include LQT2, LQT3, and QTc interval &gt;500 msec;</td>
</tr>
</tbody>
</table>

* Data are from the American College of Cardiology, the American Heart Association, and the European Society of Cardiology, in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Guidelines are adapted from Zipes et al.⁵²

† Levels of evidence are as follows: I, conditions for which there is evidence or general agreement, or both, that a given procedure or treatment is beneficial, useful, and effective; II, conditions for which there is conflicting evidence or divergence of opinion, or both, about the usefulness and efficacy of a procedure or treatment; IIa, conditions for which the weight of evidence or opinion is in favor of usefulness and efficacy; and IIb, conditions for which the usefulness and efficacy are less well established by evidence or opinion.

‡ Other indicators of risk may include the specific site of mutation⁴ and the postpartum period.¹⁸
Genetics...In our Waiting Rooms...and Exam Rooms

Top 10 Causes of Death

1. Heart disease
2. Cancer
3. Stroke
4. Chronic Lung
5. Accident/Injury
6. Diabetes
7. Influenza/Pneumonia
8. Alzheimer's
9. Chronic Renal dz
10. Sepsis

Diet, HTN, Tobacco
Tobacco, Pollutants
Behavior, Occupation
Diet, obesity
Infection, exposure
Aging, TV
HTN, DM, Autoimmune
Infection, Immun. def.

Socio-economic-Access

LDLR, MYH7, LMNA, SCN5a
BRCA1, BRCA2, APC, CDK4, CDH1
LDLR, ENG
AAT, CFTR, FLCN
GCK, HNF4A, HNF1
CFTR, NCF2, ADA
APP, PSEN1, PSEN2
GLA, COL4A5
ADA, CCR5
• **Genetic Testing**
  - Cost Effectiveness of genetic testing
  - Evolution of genetic testing
  - Roles of genetic testing
  - Patient impact of genetic testing
Some Clues To Genetic Disorders

• ‘Known’ Genetic Disorder

• Positive Family History

• Premature presentation

• Unusual presentation

• Unexpected natural progression

[Breast Cancers in two +60 year-old patients (BRCA2)]

[Breast Cancers in two +60 year-old patients (BRCA2)]

[Cerebral edema in 39 year-old ‘healthy’ male after pharyngitis → high NH4 → OTC deficiency]

Treatment / Management

• **Prophylactic Surgery**
  – Hereditary cancers

• **Avoidance of volatile anesthetics**
  – Malignant Hyperthermia

• **‘Personalized’ Medication Regimens**
  – Pharmacogenetics: warfarin, clopidogrel

• **Expectant screening (proactive >> reactive)**
  – Hereditary syndromes of:
    • cancers, cardiomyopathies, endocrinopathies, renal disease, and others
18 year old with ‘borderline’ ECG

QTc: 0.45
Objective 3: How to make sense of genetic testing?

Huntsman et al. NEJM 2001; 344 (25): 1904

Family history identified 2 persons ‘at 50% risk’ → negative endoscopic biopsies → surgery → 1 cancer

Had Gastrectomy based on FAMILY HISTORY

Genetic testing → 4 persons with CDH1 mutations → negative endoscopic biopsies → surgery → 4 cancers
32 y/o woman a stroke.
HPI: Presented with acute aphasia and right sided paralysis
PMH: Migraines, UTIs, recurrent epistaxis, depression, miscarriage
Meds: Venlafaxine (no oral contraceptives)
SH: no drugs, no travel
Family Hx: uncle with arteriovenous malformations (AVMs)
32 y/o woman a stroke.

**HPI:** Presented with acute aphasia and right sided paralysis

**PMH:** Migraines, UTIs, recurrent epistaxis, depression, miscarriage

**Meds:** Venlafaxine (no oral contraceptives)

**SH:** no drugs, no travel

**Family Hx:** uncle with arteriovenous malformations (AVMs)

_Pulmonary AVMs found. Genetic testing found mutation in ALK1 → hereditary hemorrhagic telangiectasia (HHT). Testing of the patient’s four children showed that three of them also had this mutation._
• Case

- 55 y/o male presents with NYHA IV CHF
- PMH: Hypertrophic cardiomyopathy at age 45
- Workup included biopsy → suggested Fabry Disease
- Fabry confirmed by enzymatic and genetic testing → α-galactosidase A mutation G328R

• Frustaci et al. NEJM 2001; 345: 25-31
Chaperone-Based Therapy
Whole-Genome Sequencing in a Patient with Charcot–Marie–Tooth Neuropathy

- 3,000,000,000bp
- 90,000,000,000 bp read
- 3,420,306 variants
- 1,165,204 near genes
- 9,069 changed proteins
- 54 in genes
- 2 in SH3TC2 gene
- 3,148 near neuro-genes
- $50,000
- **Recommended for all athletes**....geared specifically to show athletes, trainers or **anyone** where their genetic advantage lies. ...genetic markers, specifically the ACTN3 gene...R577X variant

<table>
<thead>
<tr>
<th>Test Results</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 copies of R577X variant</td>
<td>Predisposition to endurance events</td>
</tr>
<tr>
<td>1 copy of R577X variant</td>
<td>Equally suited for both endurance and sprint/power events</td>
</tr>
<tr>
<td>No variant found</td>
<td>Predisposition to sprint/power events</td>
</tr>
</tbody>
</table>
Electronic resources about Genetics (see handout)

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Thank You For Your Attention
Is There an Available Genetic Test?

• Testing Available?

• Testing Indicated?