What Should Physician Assistants Know about Genetics & Genomics?

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University of Alabama at Birmingham
“Genetics can truly claim to be the central basic science of medicine at the beginning of the 21st century.”

- Francis S. Collins, M.D., Ph.D.
  Director, National Human Genome Research Institute

14% internists and ob/gyn did not know that risk is increased
75% would provide counseling
9% refer to geneticist, 15% to oncologist or surgeon, 22% call colleague

• 57% internists and ob/gyn did not know that risk is increased
• 55% would provide counseling
• 9% refer to geneticist, 15% to oncologist or surgeon, 22% call colleague

Psychiatric Genetics: A Survey of Psychiatrists’ Knowledge, Opinions, and Practice Patterns


<table>
<thead>
<tr>
<th>Statement</th>
<th>Agree, %</th>
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<tbody>
<tr>
<td>I feel competent to discuss genetic information regarding psychiatric illness with patients and their families</td>
<td>23</td>
</tr>
<tr>
<td>I feel it is my role to discuss genetic information regarding psychiatric illness with patients and their families</td>
<td>83</td>
</tr>
<tr>
<td>My medical training has prepared me to discuss genetic information regarding psychiatric illness with patients and their families</td>
<td>15</td>
</tr>
</tbody>
</table>
DNA sequence → RNA → protein → metabolites
Genome → Transcriptome → Proteome → Metabolome
$ = Econome

Human Genome
Classical Perspective
Human Genome
Modern Perspective
Human “Phenome”

Monogenic
- sickle cell
- cystic fibrosis
- Huntington

Multifactorial
- asthma
- hypertension
- diabetes

Pharmacogenomics
- drug metabolism
- new drug targets

Cancer
- familial
- sporadic
A Tale of Two Drugs Hints at Promise for Genetic Testing
By GINA KOLATA
Published: July 11, 2000

A decade or so ago, when the revolution in genetics was getting underway, the air was heady with promises.

Gene tests, scientists predicted, would become an integral part of drug prescribing. No longer would patients find out too late that a drug did not work for them. No longer would they have to wait to see if side effects to one drug before switching to another.

Tests of their genes would make all of this clear. In the exception of a few tests for genes on certain cells, the genetics revolution has not yet happened.

The New York Times
Direct to Consumer Genetic Testing
Quality  Professionalism
Evidence-Based Medicine
Genomics  Personalized Medicine
What Should Physician Assistants Know About Genetics?

1.
2.
3. Family history can be a clue to risk.
Hemochromatosis

- Excessive Fe absorption
- Fe overload in tissues
  - cirrhosis
  - diabetes mellitus
  - heart failure
  - bronzing of skin
  - hypogonadotrophic hypogonadism
  - more severe manifestations in males
- Treat with phlebotomy
  - 1 pt = 250 mg Fe
**DISEASE-RELATED CONDITIONS IN RELATIVES OF PATIENTS WITH HEMOCHROMATOSIS**

ZANETA J. BULAJ, M.D., RICHARD S. AJIOKA, PH.D., JOHN D. PHILLIPS, PH.D., BERNARD A. LASALLE, B.S., LYNN B. JORDE, PH.D., LINDA M. GRIFFEN, B.A., CORWIN Q. EDWARDS, M.D., AND JAMES P. KUSHNER, M.D.

*N Engl J Med 2000;343:1529-35*

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>CLINICALLY UNSELECTED HOMOZYGOUS RELATIVES OF PROBANDS (N=214)</th>
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<tbody>
<tr>
<td></td>
<td>MEN</td>
</tr>
<tr>
<td>No. of subjects</td>
<td>113</td>
</tr>
<tr>
<td>Liver biopsies — no. of subjects</td>
<td>78</td>
</tr>
<tr>
<td>Disease-related conditions — no. of subjects*</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>14</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>13</td>
</tr>
<tr>
<td>Aminotransferase elevation</td>
<td>11</td>
</tr>
<tr>
<td>Arthropathy</td>
<td>5</td>
</tr>
<tr>
<td>Subjects with at least 1 disease-related condition — no. (%)</td>
<td>43 (38)</td>
</tr>
<tr>
<td>Other clinical findings — no. of subjects</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>3</td>
</tr>
<tr>
<td>Hypogonadotrophic hypogonadism</td>
<td>4</td>
</tr>
<tr>
<td>Cardiac arrhythmia†</td>
<td>10</td>
</tr>
<tr>
<td>Portal hypertension with splenomegaly</td>
<td>9</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>2</td>
</tr>
<tr>
<td>Porphyria cutanea tarda</td>
<td>1</td>
</tr>
</tbody>
</table>

*If a subject had more than one of the foregoing only the condition listed first.

†Arrhythmia was documented by electroc...
Legal Precedents

• **Pate v. Threkel, 1995**
  – Pate discovered she had medullary thyroid carcinoma 3 years after her mother was treated for disease. She sued physician arguing he had a duty to warn her mother of genetic transmission and recommend testing children.
  – Court found no duty to warn children directly, but did find duty to warn the patient about familial implications

• **Safer v. Estate of Pack, 1996**
  – Safer’s father tx for colon cancer associated with adenomatous polyposis coli. Two decades later, once she was diagnosed with colon cancer, she sued her father’s physician’s estate for a failure to warn.
  – Court upheld a duty to warn those at-risk of avoidable harm from genetic disease
What Should Physician Assistants Know About Genetics?

1. 
2. Clinical decisions will increasingly rely on the results of genetic tests.
3. Family history can be a clue to risk.
Breast Cancer Prevention

The New England Journal of Medicine

RISK-REDUCING SALPINGO-OOPHORECTOMY IN WOMEN WITH A BRCA1 OR BRCA2 MUTATION

Nobuhisa Kato, M.D., Jaya M. Satagopan, Ph.D., Mark E. Robison, M.D., Lauren Schneider, M.S., Markie Hensley, M.D., Clifford A. Hudis, M.D., Nathan A. Ellis, Ph.D., Jeff Boyd, Ph.D., Patrick I. Borgen, M.D., Richard R. Barakat, M.D., Larry Norton, M.D., and Kenneth Offit, M.D., M.P.H.
Welcome to the GeneTests Web site, a publicly funded medical genetics information resource developed for physicians, other healthcare providers, and researchers, available at no cost to all interested persons. Use of this Web site assumes acceptance of the terms of use.

At This Site

- **GeneReviews**
  - Online publication of expert-authored disease reviews
- **Laboratory Directory**
  - International directory of genetic testing laboratories
- **Clinic Directory**
  - International directory of genetics and prenatal diagnosis clinics
- **Educational Materials**
  - Illustrated glossary
  - About genetic services
  - PowerPoint® slide presentations
Genetic Variation

...
Genetics in Medicine

- Disease
- Presymptomatic
- Prenatal

Birth

Genetic liability

Environmental factors
Genetics Dashboard
$w = w_0 + gG_z z$

$m_+ = m_x + i m_y \sim \gamma \int b_1(t) e^{-i \gamma G_z z t} dt = B_1(\gamma G_z z)$
What Should Physician Assistants Know About Genetics?

1. A new medical paradigm will emerge.
2. Clinical decisions will increasingly rely on the results of genetic tests.
3. Family history can be a clue to risk.
Medicine in Transformation

Two Convergent Forces

Information Technology

Genetics

“Personalized Medicine”

- Predictive testing and prevention
- Stratification of disease and targeted treatments
- Pharmacogenetics & Pharmacogenomics
$\alpha_1$-Antitrypsin Deficiency

- Inhibitor of neutrophil elastase
- Pulmonary emphysema
- Hepatic cirrhosis
- 1:2,500 Caucasians
- Carrier frequency 0.03

Targeted Therapy

Genomic Analysis
EGFr Mutation and Gefitinib Sensitivity in NSCLC Lung Cancer

NSCLC response to gefitinib

EGFr mutations

Disease Stratification
Targeted Therapy

hypertension
Pharmacogenetics

- CYP2D6 (debrisoquine hydroxylase)
  - Poor metabolizer (PM)
    - Mutations that decrease expression
      - 5-10% N.A. whites; 1-2% African Americans
  - Ultrarapid metabolizer (UM)
    - Duplications
      - 5-10% whites, 29% Ethiopians

Weinshilbaum, R., NEJM 2003;348:529
# Drugs Metabolized by CYP2D6

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesics</td>
<td>Codeine, hydrocodone, tramadol</td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td>Encainide, flecaïnide, mexiletene, propafenone</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Amitriptyline, desipramine, fluoxetine, fluvoxamine, imipramine, nortriptyline, paroxetine</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>Chlorpheniramine, diphenhydramine, promethazine</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Haloperidol, perphenazine, thidiazine</td>
</tr>
<tr>
<td>Beta Blockers</td>
<td>Carvedilol, metoprolol, propranolol, timolol</td>
</tr>
<tr>
<td>Cough suppressants</td>
<td>Codeine, dextromethorphan</td>
</tr>
</tbody>
</table>
Warfarin Pharmacogenetics

pharmacokinetics

pharmacodynamics

www.pharmgkb.org
Drug Toxicity

Polymorphism in KCNE2 potassium channel (1.6%) found in patient who developed prolonged QT while treated with Bactrim

Pharmacogenetic Testing

Imagine personalized medicine... the era of matching the right patient with the right treatment is dawning...

X PRIZE

- What is an X PRIZE?
- Why X PRIZEs Work
- Ansari X PRIZE
- Archon X PRIZE for Genomics
- Automotive X PRIZE
- Future X PRIZEs

The era of personalized medicine is dawning

As scientists gain knowledge from mapping the Human Genome, they will also find new ways to treat and even prevent disease. To build the library of information necessary to advance the field of genomic medicine, it is imperative that we develop DNA sequencing technology that is faster and affordable.

To stimulate breakthrough innovation in the field of genomic sequencing, the X PRIZE Foundation has launched a global competition with a $10 million prize for the winner of the Archon X PRIZE for Genomics.

Learn more about the Archon X PRIZE for Genomics.

The $1,000 Genome Sequence
Your patient is a slow metabolizer of azathioprine.

| General: | No weight loss, night sweats, fatigue |
| Skin:     | No rash, itching jaundice, changes in pigmentation or texture, nails, psoriasis |
| Head:     | No headache, dizziness, trauma |
| Ears:     | No hearing loss, earache, tinnitus, discharge |
| Eyes:     | No difficulty seeing, inflammation, diplopia, lacrimation |
The future of healthcare?
Report 1
Learning Objectives for Medical Student Education
Guidelines for Medical Schools

Medical School Objectives Project
January 1998
<table>
<thead>
<tr>
<th>Clinical Years Now</th>
<th>Residency 5 years +</th>
<th>Practice 10 years +</th>
</tr>
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<tbody>
<tr>
<td><strong>Prevention</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Newborn screening for inborn errors of metabolism and other disorders</td>
<td>• Expanded newborn screening with tandem mass spectrometry</td>
<td>• Wide array of disorders subject to newborn screening</td>
</tr>
<tr>
<td>• Carrier screening for hemoglobinopathies, lysosomal storage disorders, cystic fibrosis</td>
<td>• Increased number of prenatal carrier screens</td>
<td>• Routine use of proteomic screens for very early detection of common cancers</td>
</tr>
<tr>
<td>• Presymptomatic testing for breast, ovarian, colon cancer</td>
<td>• Expanded scope of cancer screening and presymptomatic testing</td>
<td>• Increasing use of screening for risk for common disorders to achieve risk stratification and implement prevention strategies</td>
</tr>
<tr>
<td>• Limited proteomic screening for cancer</td>
<td>• Limited use of screening panels for common disorders, such as cardiovascular disease or dementia</td>
<td></td>
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<table>
<thead>
<tr>
<th>Diagnosis</th>
<th></th>
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<tbody>
<tr>
<td>• High resolution cytogenetic analysis for constitutional changes and cancer</td>
<td>• Use of microarrays to diagnose subtle chromosomal abnormalities</td>
<td>• Use of panels of molecular tests to stratify common disorders such as asthma or hypertension</td>
</tr>
<tr>
<td>• Molecular diagnostic tests for limited number of monogenic disorders</td>
<td>• Increasingly routine use of molecular testing for wide range of monogenic disorders</td>
<td>• Routine molecular characterization of tissues in pathology</td>
</tr>
<tr>
<td>• Prenatal diagnosis by amniocentesis and CVS</td>
<td>• Increasing use of expression microarrays in histopathological diagnosis</td>
<td>• Use of panels of tests to achieve precise diagnosis of monogenic and chromosomal disorders</td>
</tr>
<tr>
<td></td>
<td>• Use of new modes of prenatal testing, such as preimplantation testing</td>
<td></td>
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<table>
<thead>
<tr>
<th>Treatment</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>• Limited pharmacological treatment of monogenic disorders (e.g., lysosomal disorders)</td>
<td>• Increasing array of monogenic disorders amenable to treatment</td>
<td>• Routine use of pharmacogenetic profiling</td>
</tr>
<tr>
<td>• Limited use of pharmacogenetic testing (e.g., TPMT)</td>
<td>• Expanded panel of pharmacogenetic tests (e.g., CYP2D6)</td>
<td>• Stratification of common disease and selection of specifically targeted therapies</td>
</tr>
<tr>
<td>• New forms of chemotherapy based on knowledge of cancer biology</td>
<td>• Increasing number of new cancer-specific therapies</td>
<td>• Limited routine use of gene therapy</td>
</tr>
<tr>
<td>• Experimental gene therapy protocols</td>
<td>• Continued experimentation with gene therapy</td>
<td>• Use of expression arrays to determine treatment strategies widespread</td>
</tr>
<tr>
<td></td>
<td>• Use of expression arrays to determine treatment strategies for certain diseases</td>
<td></td>
</tr>
</tbody>
</table>
Pedagogy

- Genetics is a natural integrator
- Teach things that matter
- Recognize the importance of role models
2002

CAD
age 57

J.L.
2007

J.L. is admitted to the hospital. He rules out for myocardial infarction by enzymes and electrocardiography. Family history reveals two siblings who died suddenly and a child who has had a syncopal episode. Blood is sent for a DNA test and J.L. is found to have a mutation in the $\beta$ cardiac myosin heavy chain gene. A.L. is found to have the same mutation, but it is not present in B.L. or C.L. A.L. is started on a program of regular monitoring by echocardiography.
A.L.’s pediatrician learns of a family history of sudden death on his father’s side. He arranges for a blood specimen to be sent to the laboratory for a panel of tests involving genes associated with cardiac dysfunction. A.L. is found to have a mutation in the $\beta$ cardiac myosin heavy chain gene. The same mutation is found in J.L. A.L. is started on a program of monitoring by echocardiography. An echocardiogram done in J.L. reveals signs of advanced hypertrophic cardiomyopathy. He is started on a new $\beta$ blocker medication, and is advised to consider implantation of a defibrillator.
In the course of a routine primary care visit, D.L. is noted to have a family history of early unexplained death (her mother and maternal aunt). She is tested for a set of risk factors known to predispose to early death and is found to have a mutation in the β cardiac myosin heavy chain gene. She is started on a new class of medication known to prevent the occurrence of hypertrophic cardiomyopathy. Four of her children are also found to carry the mutation. They, too, are started on medication and a program of regular monitoring.
Medical Genetics Training

• Medical Genetics
  – 2 year genetics residency
    • 2 prior years of ACGME-accredited residency
  – 5 year combined internal medicine-genetics or pediatrics-genetics program
  – ACGME-accredited, ABMG certification

• Genetic Counseling
  – 2 years masters program
  – ABGC Certification
# Genetics in Medicine

<table>
<thead>
<tr>
<th></th>
<th>Primary Care</th>
<th>Specialist</th>
<th>Medical Geneticist</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single Gene or Chromosomal</strong></td>
<td>recognize signs and symptoms; make referral; support family; longitudinal care</td>
<td>manage specific problems</td>
<td>diagnosis; counseling; longitudinal care</td>
</tr>
<tr>
<td><strong>Major Gene Multifactorial</strong></td>
<td>Appreciate role of family history; arrange testing and referral to specialist as needed; provide longitudinal care</td>
<td>Diagnosis and management of system-specific problems</td>
<td>Advise on interpretation of test results; genetic counseling; evaluation of complex cases</td>
</tr>
<tr>
<td><strong>Complex Multifactorial</strong></td>
<td>Use of genetic tests to guide treatment</td>
<td>Use of genetic tests to guide treatment</td>
<td>Reservoir of knowledge and handling of complex cases</td>
</tr>
</tbody>
</table>
• Education of health professionals and the general public
• Access to information
• Tools for screening, education
• Protection of individual rights and privacy
• Knowledge of outcomes
• Development of new prevention strategies and treatments
We tend to overestimate the effect of a technology in the short run and underestimate the effect in the long run.

Amara’s Law