Genomics and Precision Medicine, Its More than Skin Deep

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• Susan LeLacheur, DrPH, PA-C
1. Describe advances and gaps in clinical applications of precision medicine.

2. Discuss dilemmas in teaching physician assistants about genomics and precision medicine as the scientific, legal and ethical context rapidly changes.

3. Describe ways of teaching students to incorporate modern understanding of genomics along with social, behavioral and environmental factors into personalized care for the patient.
What is Precision and Personalized Medicine?

The current landscape and impact of precision medicine on the four (4) P's

Predictive Analytics
- Artificial Intelligence
- Big Data, Deep Learning Intelligence

Personalization
- Genomics
- Prevention
- Participatory
Human Genome Project and the Precision Medicine Initiative
What is included
What is

- Artificial Intelligence
- Global Metabolomics Assessment
- Research: Undiagnosed Disease Network
- Genomics
- Microbiome testing
- EMR System Integrations
- Pharmacogenetics
- Education: Future and Current Healthcare workforce
Current State of Precision Medicine
Clinical Applications

Cut

Ibuprofen

DIE

Suicide

Advil

Never

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Genetic Testing

- Predictive
- Diagnostic
- Forensic
- DTC
- Preimplantation
- Screening: Carrier, Prenatal, Newborn
- Pharmacogenetic
Human Genomic Sequencing: What is all the hype about!

- Genotype Testing
  - Direct To Consumer (DTC)
- Whole Exome Sequencing
- Whole Genome Sequencing
Pharmacogenetics

• Opioid Crisis = What about pharmacogenomics?
• CYP2D6 = Codeine, Tramadol. CPIC guidelines 2014
• Anti-depressants?
• CYP2D6 & CYP2C19 = CPIC guidelines SSRI, 2015, TCA(2016),
• Others through CYP2D6 & CYP2C19 = : Ondansetron (2017) Tamoxifen (2018)
• Warfarin metabolism!!! = CYP2C9, VKOR1, CYP4F2, rs12777823
**Effect of CYP2D6 Genotype on Opioid Response:**
- Cytochrome P450 2D6 (CYP2D6) is a drug-metabolizing enzyme expressed primarily in the liver.
- CYP2D6-mediated opioids (oxycodeone, tramadol, hydrocodone, codeine) are converted to more potent active metabolites by the CYP2D6 enzyme.
  - CYP2D6 metabolizes about 10% of oxycodone into the more potent compound, oxymorphone.
  - CYP2D6 UMs make MORE oxymorphone (may have increased risk of toxicity).
  - CYP2D6 IMs and PMs make LESS oxymorphone (may have decreased efficacy).

**How to Interpret CYP2D6 Test Results:**

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Population Prevalence</th>
<th>Genotype</th>
<th>Enzyme Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor Metabolizer (PM)</td>
<td>~1-10%</td>
<td>No functional alleles present</td>
<td>Absent</td>
</tr>
<tr>
<td>Intermediate Metabolizer (IM)</td>
<td>~2-11%</td>
<td>1 reduced-function AND 1 nonfunctional allele.</td>
<td>Decreased</td>
</tr>
<tr>
<td>Extensive/Normal Metabolizer (EM)</td>
<td>~77-92%</td>
<td>2 alleles with full or reduced function OR 1 fully functioning allele AND 1 nonfunctional or reduced-function allele.</td>
<td>Normal</td>
</tr>
<tr>
<td>Ultra-Rapid Metabolizer (UM)</td>
<td>~1-2%</td>
<td>&gt; 2 functional alleles</td>
<td>Increased</td>
</tr>
</tbody>
</table>


- A patient's CYP2D6 lab report will reflect the information in this table. For example, it may read as “CYP2D6 *1/*1 (extensive metabolizer phenotype); normal CYP2D6 enzyme activity.”

**How to Convert from One Opioid to Another**
1. Determine the amount of current opioid(s) patient has taken in a 24-hr period that effectively controlled pain. If uncontrolled, use amount taken in past 24-hr period.
2. Calculate “Opioid Equivalent Dose” using table (on right).
3. If pain was effectively controlled on current opioid, reduce the new opioid daily dose by 25-50% for cross tolerance.
4. If pain was uncontrolled on the current opioid, use 100-125% of the equalangetic dose.
5. Divide the calculated daily dose of new opioid by the number of doses per day to determine the individual dose

<table>
<thead>
<tr>
<th>Opioid Equivalent Doses</th>
<th>Oral Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycodeone</td>
<td>16 mg</td>
</tr>
<tr>
<td>Morphine</td>
<td>30 mg</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>7.5 mg</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>16 mg</td>
</tr>
</tbody>
</table>

• Clinical instruments
• Sequencing
• Analysis
Direct-To Consumer Test and Consumer Controlled Market

• Direct to Consumer

• Consumer Controlled Consent
Nutrigenomics
HealthCare System Integrations

Geisinger Health

MyCode®
Scorecard

Johns Hopkins inHealth
No more "One Size Fits All" Approach

New Paradigm Shift in Treatment
Transitioning From the ‘one-size-fits-all’ to ‘precision medicine’ model with multi-level patient stratification.

One-size-fit-all Medicine

Stratified Medicine

Precision Medicine

Patients are grouped by:
- Disease Subtypes
- Risk Profiles
- Demographics
- Socio-economic
- Clinical Features
- Biomarker
- Molecular sub-populations

Individual patient level:
- Genomics and Omics
- Lifestyle
- Preferences
- Health History
- Medical Records
- Compliance
- Exogenous Factors

Precision medicine ensures delivery of the right intervention to the right patient at the right time.

Companion Diagnostic (CDx) Biomarker

Therapy (Rx + Dx = CDx)

Each Patient Benefits From Individualized Treatment
Key Clinical Ethics Concerns

**Autonomy**
- The capacity to act on your own decisions freely and independently
- Respect a patient’s dignity/right to make decisions
- (What is adequate Informed Consent to genetic testing?)

**Justice**
- Treating patients fairly and equitably
- (How do we ensure that all patients are treated fairly?)

**Beneficence/Non-maleficence**

**First do no harm**
- Risk/Benefit Analysis
- (How do we engage in genetic testing responsibly?)

**Privacy/Confidentiality**
- (What are the limits to these duties?)

Author: Joe Heller (2000)
Autonomy

- At what age is an individual competent to consent?
- Should newborns be given a chance to decide later in life?
- Do family members have a right to know a relative’s genetic test result?
- What if a patient does not want to know genetic test results? (long term probabilistic vs. lifesaving knowledge)
Do No Harm

• Testing
  • When do we provide testing?
  • How do we prevent the use of unnecessary procedures?

• Counseling
  • How do we provide genetic/genomic information responsibly?
    • Psychological harms
  • When do we provide counseling?
    • Some proteins reveal genetic risk—counsel before or after protein testing?
Molly Nash, 6, receives a stem cell transplant from her IVF conceived brother who was tested for HLA compatibility, 2007.
Is it possible to treat patients fairly when some patients have variants of unknown significance?

Why do some doctors order genetic tests for African-American women at lower rates?
Diversity & Inclusion

96% of participants in genome-wide association studies of European descent (2009) Participants of Asian ancestry increased to 20% African American and Latino participation under 4%

Population descriptors
• 'black cases' and 'sub-Saharan African', were often used to describe people of African ancestry.
• More often “geographically specific and informative descriptions were those used for samples of European origin. . .”
Genetic Tests for a Heart Disorder Mistakenly Find Blacks at Risk

By DENISE GRADY  AUG. 17, 2016

Genetic tests for an inherited heart disorder are more likely to have incorrect results in black Americans than in whites, according to a new study that is likely to have implications for other minorities and other diseases, including cancer.

Mistakes have been made because earlier research linking genetic traits to illness did not include enough members of minority groups to identify differences between them and the majority white population or to draw conclusions about their risks of disease.

The new study, published Wednesday in The New England Journal of Medicine, focused on hypertrophic cardiomyopathy — a thickening of the wall of the heart that can cause abnormal rhythms and sudden death. The condition often has no symptoms, but can cause young athletes to pass out or even die during the intense activity of their sport. It can be caused by inherited mutations in one of 10 to 20 genes, and affects one in 500 people in the United States. More than 1,000 mutations have been linked to the condition.
Self-perpetuating Bias

Bias in Datasets: datasets can become unintentionally biased through a) a lack of cohort diversity, b) technical processes of data collection and cleaning, and c) the specific incorporation of electronic health record data.

Bias in Outcomes: the outcomes of precision medicine research can be discriminatory in many ways. These include a) too much focus on individual responsibility for health, b) the marginalization of those population groups with lower health literacy or in less resourced areas, and c) the potential to shift the accepted forms of biomedical research.
ORIGINAL ARTICLE
Ethnicity-specific pharmacogenetics: the case of warfarin in African Americans

W Hernandez¹, ER Gamazon¹, K Aquino-Michaels¹, S Patel², TJ O’Brien³, AF Harralson³,⁴, RA Kittles⁵, A Barbour⁶, M Tuck⁷, SD McIntosh⁶,⁷, JN Douglas⁷, D Nicolae¹, LH Cavallari² and MA Perera¹

Using a derivation cohort (N = 349), we developed the first warfarin dosing algorithm that includes recently discovered polymorphisms in VKORC1 and CYP2C9 associated with warfarin dose requirement in African Americans (AAs). We tested our novel algorithm in an independent cohort of 129 AAs and compared the dose prediction to the International Warfarin Pharmacogenetics Consortium (IWPC) dosing algorithms. Our algorithm explains more of the phenotypic variation (R² = 0.27) than the IWPC pharmacogenomics (R² = 0.15) or clinical (R² = 0.16) algorithms. Among high-dose patients, our algorithm predicted a higher proportion of patients within 20% of stable warfarin dose (45% vs 29% and 2% in the IWPC pharmacogenomics and clinical algorithms, respectively). In contrast to our novel algorithm, a significant inverse correlation between predicted dose and percent West African ancestry was observed for the IWPC pharmacogenomics algorithm among patients requiring ≥60 mg per week (β = −2.04, P = 0.02).

The Pharmacogenomics Journal (2014) 14, 223–228; doi:10.1038/tpj.2013.34; published online 10 September 2013

Keywords: African Americans; algorithm; CYP2C9; polymorphisms; VKORC1; warfarin
Figure 1 Map showing estimates of the percentage of European contribution to several African American communities throughout the US. The percentage of European contribution to several African American samples within the continental US varies tenfold, from 3.5% in the isolated Gullah-speaking Sea Islanders from South Carolina to 35% in Seattle. Reproduced from Parra [15].

“One of the great truths to emerge from this triumphant expedition inside the human genome is that in genetic terms, all human beings, regardless of race, are more than 99.9 percent the same.”
20. Carbamazepine, also known as and referred to herein as Carbatrol, is a drug known to have an increased potential to cause life-threatening disease to persons of Asian heritage. Specifically, it was and is known in the medical community that persons of Asian descent who take the drug have a much greater tendency to develop Stevens-Johnson Syndrome. Stevens-Johnson Syndrome is a life threatening toxic skin condition in which cell


The use of ancestry in the drug labeling creates potential safety problems for patients, cost concerns for patients and insurers, and potential stigmatization of a drug that has been used for years to treat complex neurological illnesses. Categorizing people for personalized medicine must be done, if at all, in a scientifically valid, sensitive, and ethical manner.

Privacy/Confidentiality

- The interest of others
  - Public or Employer Interest
- Examples
  - Eddie Curry and Ryan Clark
    - Fatal heart condition
  - Sickle cell trait
  - Employee DNA testing
    - Prohibited by GINA
Ethical Recommendations

Foreseeable, identifiable victim & serious risk
• A clinician’s duty may be fulfilled by encouraging patients to communicate with relatives - American Society of Clinical Oncology, 2010
Ethical Recommendations

• Should the physician have a duty to find and notify relatives?
• The AMA Code of Medical Ethics, Opinion 2.131 (Based on 2003 Report)
  • Finding and notifying family members is not a physician’s duty
  • Physicians should inform patients in advance of what they expect them to disclose to their families and be available to assist in this communication
Ethical Recommendations
The Committee on Genetic Risks of the Institute of Medicine (1994)

• Confidentiality may be breached, and the relatives informed of the risks when:
  • Attempts to elicit voluntary disclosure fail
  • There is a high probability of irreversible or fatal harm to the relative
  • The disclosure of the information will prevent harm
  • The disclosure is limited to the information necessary for diagnosis or treatment of the relative
  • There is no other way to avert harm
Law

• Example questions
  • Can you be sued for malpractice for failing to order a genetic test?
  • What is the legal standard for ordering genetic testing services?
  • What is the legal standard for following drug label guidance?
  • What is the legal standard for discussing genetic test results with patients?
Can you be sued for medical malpractice?

- Failure to diagnose, interpret, offer, disclose
- Examples
  - Negligent delivery of a newborn
  - Failure to completely review the medical record
  - Failure to order a genetic test or refer to a specialist
  - Adverse drug reactions
  - Unsuccessful tumor treatment
Keel v. Banach (Ala. 1993)

- Duty to perform standard of care to patient
  - Prudent care /custom, lit, state of the science?
- SOC Breach
  - Failed to detect risk of abnormality before or during pregnancy.
- Causation
  - Proximate cause: negligently performed or omitted counseling, prenatal testing → lack of informed decision re conception
- **Court:** Parents may maintain action for wrongful birth if the result of negligent failure of the attending prenatal physician to discover and inform them of the existence of fetal defects.
Molloy v. Meier (Minn. 2004)

• Medical Negligence (Wrongful Conception)

• Facts
  • failure to diagnose Fragile X in 1st daughter (with ex husband) → 2nd child, son
  • Pediatrician noticed developmental delays; tests failed to reveal source; reasonable to test for Fragile X but excluded – general report negative.
    • Series of Drs failed to diagnose, incl neurologists (Dr. Backus & Green)
Expert testimony: pediatrician and pediatric neurologist

The prevailing standard of care in the medical community with respect to testing and counseling for genetic disorders is that if patient exhibits the symptoms of Fragile X and has a family history of mental disability – **patient should be tested for Fragile X**

Physician has additional duties to (a) follow up to confirm that the tests are performed and (b) provide genetic counseling to child’s family.

Molloy v. Meier (Minn. 2004)
• Plaintiffs argue on Appeal
  • Duty arising from Dr-patient relationship
    • Requires warning mother about pregnancy risks as carrier of Fragile X.
    • Foreseeability of injury requires Dr. to warn others of a patient’s genetic disorder (i.e. 3rd party family members)
Additional Legal Considerations

- Negligence (*Duty, breach of duty, injury, causation*)
  - Professional Guidance
  - Statutes/Regulations
  - Cases
- Health Insurance Portability & Accountability Act (HIPAA)
- Family Educational Rights and Privacy Act (FERPA)
- GINA versus the American with Disabilities Act (ADA)
  - When does a genetic mutation become a disability?
- Insurance only covers disabilities & disease
### What will hold up in Court?

- Providing an “ordinary standard of care”, which
  - Includes the highest possible degree of vigilance, prudence, and thoughtfulness.
- Evidence that patient was warned.
- Evidence of consultation with specialist.

### When is it too soon to test?

- Is there enough clinical evidence?
- Standard in the field?
- Are there other equally efficient methods that can be employed?

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**Application to Physician Assistants**
Emerging Concerns

• Early adoption by consumers (Patient Right to know?)
• Blurred lines between research and discovery (i.e., genomic incidental findings)

Figure 2: Charts the most significant increases and declines in ELSI in PGM publications about main ELSI topics during a four year period.

Callier, S. 2015
I don't want people having my DNA!!!


  - *Even if you never tested you are likely to be identified through cross referencing of anonymized DNA data with public datasets!*
Genetic Information Nondiscrimination Act. of 2008: GINA

- Protects against discrimination based on genetic information.
  - Employment
  - Health Insurance
- Does not protect discrimination with
  - Life, long-term, or disability insurance
  - Health benefits of military and federal government employees,
  - Benefits of Veterans Health, or Indian Health Service

This Photo by Unknown author is licensed under CC BY-NC-ND.
GedMatch and CODIS

- Read Terms of Service for use
- Gedmatch= 2010 public gedcom DNA matching software. No terms of service initially. Opt-out is the default. (rapes, murders, FBI-Violent crimes and unidentified bodies)
- Gives information if you match any of the Law Enforcement kits.

Combined DNA Index System (CODIS)

<table>
<thead>
<tr>
<th>Kentucky</th>
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<tr>
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<td>NDIS Participating Labs</td>
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<td>Investigations Aided</td>
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Clinical Practice Guidelines
Teaching PA Students
Future for how we educate

Education will be at a more complex molecular and biological level

Critical analysis of genomic and computational literature

Guidance on how to effectively integrate emerging precision medicine with current evidence-based medicine.


• Dunseath, S., Weibel, N., Bloss, C.S., Nebeker, C., 2018a. NIH support of mobile, imaging, pervasive sensing, social media and location tracking (MISST) research: laying the foundation to examine research ethics in the digital age. NPJ digital medicine 1:20171.


• Hernandez, W., Gamazon, E.R., Aquino-Michaels, K., (...), Cavallari, L.H., Perera, M.A.


References