Personalized Medicine Technology Trends: Impact on Anesthesiology

Society for Technology in Anesthesia
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Personalized Healthcare

Personalized Care for Every Phase of Health

- Susceptibility
- Screening
- Diagnosis
- Prognosis
- Treatment

RISING DISEASE BURDEN = RISING COSTS

- Baseline Risk
- Preclinical Progress of Disease
- Clinical Disease and Progression
Personalized Medicine: Right Drug, Right Dose, The First Time
The Possibilities of Personalized Medicine
“Any sufficiently advanced technology is indistinguishable from magic”

Arthur C. Clarke

"Hazards of Prophecy: The Failure of Imagination", in Profiles of the Future (1962)
Facebook Millions of Users
Internet Data Traffic (US) Logarithmic Plot

- Petabyte per Year
- Year

Graph showing the increase in internet data traffic from 1990 to 2008.
Exponential Growth of Computing for 110 Years

Moore's Law was the Fifth, not the First, Paradigm to Bring Exponential Growth in Computing

Calculations per Second per $1000

10^{-10} 10^{-5} 10^{0} 10^{5} 10^{10} 10^{15}

 Electromechanical  Relay  Vacuum Tube  Transistor  Integrated Circuit

Year

1900  '10  '20  '30  '40  '50  '60  '70  '80  '90  2000  '08  '10

Logarithmic Plot
“We tend to overestimate what can be achieved in the short term (because we tend to leave out necessary details)

We underestimate what can be achieved in the long term (because the exponential growth is ignored)”

Ray Kurzweil—modified from Roy Amara
Growth in Genbank DNA Sequence Data

Logarithmic Plot

Base Pairs and Sequences

Year

'80 '82 '85 '90 '95 2000 '05 '08 '10

10^11 10^10 10^9 10^8 10^7 10^6 10^5 10^4 10^3 10^2
Cost per Genome

Moore’s Law

National Human Genome Research Institute
genome.gov/sequencingcosts
Whole Genome Sequence Data

Cost of whole genome sequencing to 0.1% accuracy projected continuing to decline

Whole exome sequencing now $999

Still greater accuracy of sequence needed for clinical care

Managing and annotating the data, delivering to point of patient care a challenge

Understanding the meaning will require a lot of additional research and significant costs as it develops
First Life Saved by Genome Sequencing?
Other New Applications

- Diagnosing other rare conditions thought clinically likely to be genetic in origin—has guided therapy—including “compound heterozygote” disorders

- The first “sequencing autopsy”

- Genetic characterization of cancer guiding targeted cancer therapy

- “Consumer” genomics including pharmacogenomics—some controversies—about 100,000 consumer have bought the tests over four years
Human Complexity—DNA Level Information

DNA sequence 3 billion base pairs

Genes 20,000

Genes are about 1.5% of the genome (make proteins)

Another 3.5% of the genome makes regulatory and other RNA

Single Nucleotide Polymorphisms (SNPs) 3 million
   (0.1% of genome—used in genome wide association studies)

Duplicated “Copies” Gene Sequences (12% of genome)

Copy Number Variation (0.4% of genome)
DNA Sequence and Common Diseases

Identical and fraternal twins used to estimate heritability of common diseases such as diabetes, asthma, schizophrenia, coronary artery disease.

Hope was that genome wide association studies (GWAS) with one million SNPs would explain a lot of the heritability.

However, only 10% of heritability explained thus far for most common diseases (macular degeneration risk best explained).

Thus far about as good as taking a good family history.
Human Complexity—DNA Sequence Information
What Might Explain the “Heritability Gap”

Copy number variation

Maternal or fraternal inheritance effects

DNA modifications that inactive or activate genes

Somatic cell mutation processes
Contribution of Different Categories of “Omics” Information to Clinical Decisions: Undergoing Intense Investigation and Logarithmic Data Growth

- Clinical “Phenotype” (History, Physical)
- Lab “Phenotype” (Biochemical & Imaging)
- Genomics
- Epigenomics
- RNA expression
- Proteomics
- Metabolomics

All Lab Tests for Normal and Diseased Tissues
DNA Sequence: Predictive Pharmacogenomics

- Succinylcholine
- Inhalational agents
- Clopidogrel activity and dosing—ongoing in Vanderbilt Cardiac Catheterization for clinical care, for last year and a half
- Warfarin dosing
- Statins induced myopathy
- Tamoxifen activity
- Hepatitis C drug activity
- Azathioprine toxicity
- Beta adrenergic receptor agonist and antagonists?

DNA sequence level information dose predict some of the variable metabolism and resultant efficacy or safety of a number of drugs investigated thus far—a relative success story thus far
PREDICT
Pharmacogenomic Resource
For Enhanced Decisions
In Care & Treatment
Prospective Genetic Testing
Using the Prognostic Model

Prognostic Model identifies patients who are highest risk for starting warfarin, clopidogrel, or statin therapy within the next three years as candidates for preemptive genotyping.

Factors include:

- Age, gender, race, and BMI when height is available (or weight when BMI is not available)
- History of…Type II Diabetes, coronary disease, atrial fibrillation, hypertension, atherosclerosis, congestive heart failure, previous clot, and dialysis
What is Tested?

- DNA extracted from the patient's blood
- Specimen genotyped for 184 common polymorphisms within 34 genes associated with drug absorption, distribution, metabolism, and excretion

Illumina Vera Code ADME Core Panel Panel Assay
# FDA Labels with Pharmacogenomic Biomarkers

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<thead>
<tr>
<th>Cytochrome P450</th>
<th>Other</th>
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<tbody>
<tr>
<td>Quinidine</td>
<td>Simvastatin*</td>
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<td>Carvedilol</td>
<td>Azathioprine*</td>
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<td><strong>Clopidogrel</strong>*</td>
<td><strong>Warfarin</strong>*</td>
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<td>Metoprolol</td>
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<td>Ticagrelor</td>
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<td><strong>Tamoxifen</strong>*</td>
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<td><strong>Tacrolimus</strong>*</td>
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Estimated Adverse Events Prevented Over 5 years

Abacavir 3
Azathioprine 17
Clopidogrel 79
Simvastatin 19
Tamoxifen 15
Warfarin 265
Total 398
Preemptive Genetic Testing Launched

Prognostic Model testing began early 2012 in several outpatient clinics

- Internal Medicine—Medical Center East (MCE) Adult Primary Care Ste I-IV & Hillsboro Medical Group, One Hundred Oaks (OHO), Green Hills Clinic, Edward Curd Lane in Franklin
- VHVI & Cardiology—cardiac catheterization lab, MCE, OHO, Franklin-TN, Murfreesboro
- Eskind Adult Diabetes
- MyHealthTeam at Vanderbilt (MHTAV)

Represent over 300 providers
PREDICT information flow

Illumina BeadXpress Molecular diagnostics

Patient Summary Service (PSS)

StarPanel

Horizon Expert Orders (HEO)

RxStar

Plavix Dashboard

MyHealth at Vanderbilt
PREDICT Program Evolution

Project Planning

Project Team:
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Jennifer Mitchell
Erica Bowton
Jonathan Schildcrout
Wendy Kiepek
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Yaping Shi
Lijun Wang
Dario Giuse
Ioana Danicu
Jana Shirey-Rice
Gladys Garrison
Alan Bentley
Hassan Naqvi
Jeannine Courtney

Full Scale:

Integration into operations

Medical tech staff
Collin Mothupi
BioVU

- De-identified ongoing medical record
- Matched DNA sample (gradually being partially sequenced)
- Research tool including for genetic associations (with IRB controls)
- Unique resource for research
- Match a well defined clinical condition (“phenotype”) to DNA sequence information (“PheWAS”)
MyCancerGenome.Org

- Informatics approach matching genetic tests on cancer tissue to specific genetically targeted therapies

- Includes matching to clinical trials, for genetically targeted drugs in development

- Implemented at Vanderbilt - Ingram Cancer Center with results incorporated into StarPanel / StarChart
Impact of Whole Genome Sequencing for Anesthesiology

We will know our patients’ genetic risk factors including:

- Pseudocholinesterase deficiency—implications for succinylcholine and cocaine use in the operating room
- Malignant hyperthermia
- Codeine metabolism—genetics clinically most important now for maternal use passing on to newborns
- Oxycodone metabolism
- Morphine metabolism
- Risk factors for common diseases with anesthetic and perioperative implications
Impact of Whole Genome Sequencing for Anesthesiology Translational Research

- Ask association of a heritable clinical condition or perioperative outcomes with gene sequence, with large numbers of individuals de-identified medical records

- Examples:
  - beta-blocker perioperative use?
  - post-operative cognitive dysfunction?
  - predicting the difficult airway based on the medical record before the patient is seen?
Further in the Future

Real time diagnosis and monitoring of the following rapidly developing information sources in fluids and tissues:

- epigenome
- RNA (transcriptome)
- protein (proteome)
- metabolome
- microbiome

This complex information will power better clinical and healthcare decisions
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Ray Kurzweil—modified from Roy Amara
Interested in Learning More About New Digital Technologies in Medicine?

View Online Eric Topol’s Fall 2011 Vanderbilt Discovery Lecture
Thank you for your time and attention!

Your questions and discussion?