Genomic Medicine in Vermont

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Other Disclosures

- No Conflicts of Interest
- Perspectives
  - Academic chair
  - Molecular pathologist for 22 years
Outline

- What is genomic medicine?
- Why use genomic medicine now?
- Genomic medicine applications
- Genomic medicine in Vermont
Outline

- What is genomic medicine?
  - Why use genomic medicine now?
  - Genomic medicine applications
  - Genomic medicine in Vermont
The Human Body is Composed of Cells
Each Cell Does a Lot of Work

- Respond to Signals from the Outside
- Make Energy for Its Work
- Grow & Make New Cells
- Specific Work of the Cell
- Die if Old or Not Working Right

Diagram of a Cell
DNA Directs the Cell Work

DNA in the Nucleus

DNA Genes Make Proteins that Do Cell Work

DNA Makes RNAs that Regulate Genes
Gregor Johann Mendel (1822 – 1884)
PHENOTYPE
(What We See)

(a) Self-fertilization of parent stocks

100% yellow progeny
100% green progeny

(b) Cross-fertilization

P₁

F₁

100% yellow progeny (hybrids)

(c) Self-fertilization

F₂

75% yellow progeny
25% green progeny
PHENOTYPE: Blue Eyes  Brown Eyes

GENOTYPE: bb  BB or Bb
Recessive: b  Dominant: B

Physical Features
**GENOTYPE**

*CFTR* Gene (DNA)

**PHENOTYPE**

CFTR wild type protein ion transport normal

→ Healthy

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Single Gene Genetic Diseases
Jim Fixx
5’10”, 150 lbs
Marathon runner
Promoted healthy lifestyle
Died at 52 of MI while running
Father died at 43 of MI

Winston Churchill
5’8”, 270 lbs
Did not exercise
Smoked
Unhealthy lifestyle
Died at 90

Multifactorial Common Diseases
Cancer Genomics

Normal  \rightarrow  Adenoma  \rightarrow  Cancer

Loss of 18q

APC  \rightarrow  KRAS  \rightarrow  SMAD4  \rightarrow  TP53

CDC4  \rightarrow  Wnt  \rightarrow  BRAF  \rightarrow  CDC4  \rightarrow  BAX

Signaling

KRAS  \rightarrow  TGFBR2  \rightarrow  IGF2R

CHROMOSOMAL INSTABILITY  \rightarrow  MICROSATELLITE INSTABILITY

Increasing CIN

MMR Gene Inactivation  \&  Hypermethylation
# Leading Causes of Death in U.S.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Disease</td>
<td>596,577</td>
</tr>
<tr>
<td>Cancer</td>
<td>576,691</td>
</tr>
<tr>
<td>Chronic Lung Disease</td>
<td>142,943</td>
</tr>
<tr>
<td>Stroke</td>
<td>128,932</td>
</tr>
<tr>
<td>Accidents</td>
<td>126,438</td>
</tr>
<tr>
<td>Alzheimer Disease</td>
<td>84,974</td>
</tr>
<tr>
<td>Diabetes</td>
<td>73,831</td>
</tr>
<tr>
<td>Influenza &amp; Pneumonia</td>
<td>53,826</td>
</tr>
<tr>
<td>Kidney Disease</td>
<td>45,591</td>
</tr>
<tr>
<td>Suicide</td>
<td>39,518</td>
</tr>
</tbody>
</table>

Definition of Genomic Medicine

An emerging medical discipline that involves using genomic information about an individual as part of their clinical care (e.g., for diagnostic or therapeutic decision-making)....

Large amounts of genome (DNA) sequence (large gene panels, exome or genome) generated by next generation sequencing

National Human Genome Research Institute (NHGRI), 2012
Genomic Medicine

Molecular Medicine

Precision Medicine

Personalized Medicine
Outline

- What is genomic medicine?
- Why use genomic medicine now?
  - Genomic medicine applications
  - Genomic medicine in Vermont
Genotype: $\text{red}^0/\text{red}^0$, $\text{red}^0/\text{red}^0$, $\text{red}^0/\text{red}^0$, $\text{red}^0/\text{Y}$, $\text{red}^0/\text{Y}$

Phenotype: ♀, ♀, ♀, ♂, ♂

A Genome contains Fundamental Medical Information
Greg’s primary care physician:

“I would have never pegged you as having FMF . . .

Look at you. You have blue eyes and blond hair!”
Accurate Diagnosis Drives Effective Treatment

• Healthcare provider diagnostic ability limited by:
  – Knowledge-base
  – Biases
  – Time

Genome results may reduce diagnostic limitations
Disease Risk for Population Health Management

• Genome results may identify disease risks before onset of symptoms
  – Targeted monitoring only for at risk individuals
  – Preventive strategies, when available
Neurofibromatosis type 2
Ehlers–Danlos syndrome, vascular type
Marfan syndrome, Loeys–Dietz syndromes, and familial thoracic aortic aneurysms and dissections
Hypertrophic cardiomyopathy, dilated cardiomyopathy, catecholaminergic polymorphic ventricular tachycardia
Arrhythmogenic right-ventricular cardiomyopathy
Romano–Ward long QT syndrome types 1, 2, and 3, Brugada syndrome
Familial hypercholesterolemia 143890
Malignant hyperthermia susceptibility

Genome Reportable Results (ACMG)

- Hereditary breast and ovarian cancer
- Li–Fraumeni syndrome
- Peutz–Jeghers syndrome
- Lynch syndrome
- Familial adenomatous polyposis
- MYH-associated polyposis
- Von Hippel–Lindau syndrome
- Multiple endocrine neoplasia type 2
- Familial medullary thyroid carcinoma
- PTEN hamartoma tumor syndrome
- Retinoblastoma
- Hereditary paraganglioma-pheochromocytoma syndrome
- Tuberous sclerosis complex
- WT1-related Wilms tumor
- Neurofibromatosis type 2
- Neurofibromatosis type 2
- Marfan syndrome, Loeys–Dietz syndromes, and familial thoracic aortic aneurysms and dissections
- Hypertrophic cardiomyopathy, dilated cardiomyopathy, catecholaminergic polymorphic ventricular tachycardia
- Arrhythmogenic right-ventricular cardiomyopathy
- Romano–Ward long QT syndrome types 1, 2, and 3, Brugada syndrome
- Familial hypercholesterolemia 143890
- Malignant hyperthermia susceptibility

Genet Med 2013:15(7):565–574
Each Person is Unique

Genome → Epigenome

Epigenome → Environment

Environment → YOU

YOU → Medical Phenotype

Medical Phenotype → Healthcare Provider (EHR)

Healthcare Provider (EHR) + Patient

The University of Vermont
LARNER COLLEGE OF MEDICINE

23
A Genome is a Journey
Promise of Genomic Medicine

- Improve patient outcomes
- Improve population health, especially for families
- Improve cost-effectiveness of care

Genomic Medicine Promise aligns with Healthcare Reform Goals
Outline

- What is genomic medicine?
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- Genomic medicine in Vermont
Genomic Medicine Applications

- Cancer Genomics
- Pharmacogenomics
- Inherited Disorders
Genomic Medicine Applications

• Cancer Genomics
• Pharmacogenomics
• Inherited Disorders
Today, 609 Cancer Driver Genes Known

The cancer Gene Census is an ongoing effort to catalogue those genes for which mutations have been causally implicated in cancer. The original census and analysis was published in *Nature Reviews Cancer* and supplemental analysis information related to the paper is also available.

The census is not static but rather is updated regularly as needed. In particular we are grateful to Felix Mitelman and his colleagues in providing information on more genes involved in uncommon translocations in leukaemias and lymphomas. Currently, more than 1% of all human genes are implicated via mutation in cancer. Of these, approximately 90% have somatic mutations in cancer, 20% bear germline mutations that predispose to cancer and 10% show both somatic and germline mutations.

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Name</th>
<th>Entrez GeneId</th>
<th>Genome Location</th>
<th>Chr Bond</th>
<th>Somatic</th>
<th>Germline</th>
<th>Tumour Types (Somatic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABI1</td>
<td>abl-interactor 1</td>
<td>10006</td>
<td>10:26748570-26860863</td>
<td>10p11.2</td>
<td>yes</td>
<td></td>
<td>AML</td>
</tr>
<tr>
<td>ABL1</td>
<td>v-abl Abelson murine leukemia viral oncogene homolog 1</td>
<td>25</td>
<td>9:130835447-13085583</td>
<td>9q34.1</td>
<td>yes</td>
<td></td>
<td>CML; ALL; T-ALL</td>
</tr>
<tr>
<td>ABL2</td>
<td>c-abl oncogene 2; non-receptor tyrosine kinase</td>
<td>27</td>
<td>1:179107718-179143044</td>
<td>1q24-q25</td>
<td>yes</td>
<td></td>
<td>AML</td>
</tr>
<tr>
<td>ACKR3</td>
<td>atypical chemokine receptor 3</td>
<td>57007</td>
<td>2q37.3</td>
<td></td>
<td>yes</td>
<td></td>
<td>lipoma</td>
</tr>
</tbody>
</table>

http://cancer.sanger.ac.uk/cancergenome/projects/census/
Lung Cancer Driver Mutations
Non-small cell lung cancer, adenocarcinoma

Smokers

Non-Smokers

Braz J Med Biol Res vol.47 no.11 Ribeirão Preto Nov. 2014 Epub Sep 05, 2014
Lung Cancer Driver Mutations: Non-Smokers

- **Sorafenib, Vemurafenib, Dabrafenib**
- **Cabozantinib**
- **Neratinib, Afatinib**
- **Crizotinib**
- **KRAS G12C Inhibitors**

The diagram illustrates various lung cancer driver mutations and their corresponding inhibitors. The major categories include:

- **EGFR mutation**
- **ALK rearrangement**
- **ROS1 rearrangement**
- **BRAF mutation**
- **RET rearrangement**
- **ERBB2 mutation**
- **KRAS mutation**
- **NTRK1 rearrangement other/unknown**
1007 Tumors Tested for at least 1 Gene
733 Tumors Tested for 10 Genes
466 with Oncogenic Driver (64%)

<table>
<thead>
<tr>
<th></th>
<th>Mutation AND Targeted Therapy</th>
<th>Mutation BUT NOT Targeted Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>260</td>
<td>318</td>
</tr>
<tr>
<td>Median Survival</td>
<td>3.5 Years</td>
<td>2.4 Years</td>
</tr>
</tbody>
</table>

\[P = 0.006\]
Use of genome-directed treatments for cancer results in better outcomes with fewer side effects
Genomic Medicine Applications

- Cancer Genomics
- Pharmacogenomics
- Inherited Disorders
Pharmacogenomics (PGx)

Genetic variations can change:

- Drug metabolism (activation/inactivation)
- Drug transport (absorption, distribution, excretion)
- Drug action (variation in drug target)

Evans W, McLeod HL. NEJM 2003;348:538-549
Two Goals of Pharmacogenomics

1. Achieve Effective Dosing

2. Avoid Adverse Drug Reactions
ADRs: High Morbidity, Mortality & Cost

- 82% of adults on ≥1 medication
- 29% of adults on ≥5 medications
- 700,000 ED visits annually
- 120,000 hospitalizations annually
- $3.5B medical costs annually
- ~100,000 Americans die from an ADR annually
- ~40% of ambulatory adverse drug reaction costs preventable

http://www.cdc.gov/medicationsafety/basics.html#ref
PGx Information in 177 Drug Labels

http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm
Clinical Pharmacogenomics Implementation Consortium

PGx dosing guidelines available for 32 medications

Abacavir  Desipramine  Phenytoin
Allopurinol  Doxepin  Rasburicase
Amitriptyline  Escitalopram  Ribavirin
Atazanavir  Fluorouracil  Sertraline
Azathioprine  Fluvoxamine  Simvastatin
Capecitabine  Imipramine  Tacrolimus
Carbamazepine  Ivacaftor  Tegafur
Citalopram  Mercaptopurine  Thioguanine
Clomipramine  Nortriptyline  Trimipramine
Clopidogrel  Peginterferon alfa-2a  Warfarin
Codeine  Peginterferon alfa-2b

Use of PGx for drug selection & dosing can improve the efficacy of medications and avoid the harms and costs of adverse drug reactions
Genomic Medicine Applications

- Cancer Genomics
- Pharmacogenomics
- Inherited Disorders
Disease-Gene Associations to Date

- ~20,000 genes in human genome
- >4,000 genes with disease association in Online Mendelian Inheritance in Man (OMIM)
- Genomic approach more cost-effective than sequential testing of multiple individual genes related to a single disease
Two Inherited Disorder Applications

- Multigene Inherited Disorders (e.g. Inherited Cardiovascular Disease)
- Unidentified Inherited Disorders
11 yo Girl with Cardiac Arrest
Essex, VT in July 2012

- Cardiac arrest at swim meet
- CPR & multiple defibrillations
- PICU/CICU at UVM
- Transfer to Boston Children’s Hospital
- Genetic test performed
  - Catecholaminergic polymorphic ventricular tachycardia
  - Incidence of 1 in 10,000
  - Cause of 15% of sudden cardiac deaths in young people initiated by intense emotional or physical stress

- Tx: Implant cardioverter-defibrillator + beta blockers
Inherited Cardiovascular Disease

~1,000 sudden cardiac deaths DAILY in US

- Cardiomyopathies 50 genes
- Channelopathies/arrhythmias 28 genes
- Coronary artery disease 9 genes
- Congenital heart disease 3 genes
<table>
<thead>
<tr>
<th>Cardiovascular Disease</th>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long QT Syndrome</td>
<td>AKAP9, ANK2, CACNA1C, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNJ5, KCNQ1, SCN4B, SCN5A, SNTA1</td>
</tr>
<tr>
<td>Brugada Syndrome</td>
<td>CACNA1C, CACNB2, GPD1L, HCN4, KCND3, KCNE3, KCNJ8, SCN1B, SCN3B, SCN5A</td>
</tr>
<tr>
<td>Catecholaminergic Polymorphic Ventricular Tachycardia</td>
<td>ANK2, CALM1, CASQ2, KCNJ2, RYR2</td>
</tr>
<tr>
<td>Short QT Syndrome</td>
<td>CACNA1C, CACNB2, KCNH2, KCNJ2, KCNQ1</td>
</tr>
<tr>
<td>Hypertrophic Cardiomyopathy</td>
<td>ACTC1, ACTN2, CSRP3, GLA, LAMP2, MYBPC3, MYH6, MYH7, MYL2, MYL3, MYLK2, MYOZ2, NEXN, PLN, PRKAG2, TNNC1, TNNI3, TNNT2, TPM1, TTR</td>
</tr>
<tr>
<td>Dilated Cardiomyopathy</td>
<td>ABCC9, ACTC1, ACTN2, ANKRD1, BAG3, CSRP3, CTF1, DES, EMD, FHL1, FHL2, GATAD1, LAMP2, LDB3, LMNA, MYBPC3, MYH6, MYH7, NEXN, PLN, RBM20, SCN5A, SGCD, TAZ, TCAP, TMPO, TNNC1, TNNI3, TNNT2, TPM1, TTN, VCL</td>
</tr>
<tr>
<td>Left Ventricular Non-compaction Cardiomyopathy</td>
<td>ACTC1, CASQ2, DTNA, LDB3, LMNA, MYBPC3, MYH7, TAZ, TNNT2, VCL</td>
</tr>
<tr>
<td>Arrhythmogenic Right Ventricular Cardiomyopathy</td>
<td>DES, DSC2, DSG2, DSP, JUP, PKP2, RYR2, TMEM43</td>
</tr>
</tbody>
</table>
Two Inherited Disorder Applications

- Specific Multigene Diseases (e.g. Inherited Cardiovascular Disease)
- Unidentified Inherited Disorders
Child with Intractable IBD

- 15 month old boy with
  - Perianal abscesses & proctitis,
  - Refractory to antibiotic tx,
  - Progressing to pancolitis with colocutaneous fistula c/w Crohn disease-like illness
  - Developed diarrhea, weight loss with continued deterioration

At 30 months old, sigmoid colostomy performed & long term total perenteral nutrition started

Within 6 wks, developed bacterial sepsis
Lost to follow up until 4 years old

Admitted with malnutrition & breakdown of abdominal wall requiring daily wound care under general anesthesia

Novel approach of exome sequencing of parents & child to identify underlying cause

Analysis for recessive or de novo mutation

XIAP Mutation (X Chromosome)

Child with Intractable IBD

- DNA mutation results in a protein change in XIAP
- XIAP activates NFκB and results in increased inflammation
- Patient received BMT to replace immune function
- Doing well at 6 yrs

Clinical Exome Sequencing for Genetic Identification of Rare Mendelian Disorders

Hane Lee, PhD; Joshua L. Deignan, PhD; Naghmeh Dorrani, MS, CGC; Samuel P. Strom, PhD; Sibel Kantarci, PhD; Fabiola Quintero-Rivera, MD; Kingshuk Das, MD; Traci Toy, BS; Bret Harry, BS; Michael Yourshaw, PhD; Michelle Fox, MS, CGC; Brent L. Fogel, MD, PhD; Julian A. Martinez-Agosto, MD, PhD; Derek A. Wong, MD; Vivian Y. Chang, MD, MS; Perry B. Shieh, MD, PhD; Christina G. S. Palmer, PhD, CGC; Katrina M. Dipple, MD, PhD; Wayne W. Grody, MD, PhD; Eric Vilain, MD, PhD; Stanley F. Nelson, MD

Molecular Findings Among Patients Referred for Clinical Whole-Exome Sequencing

Yaping Yang, PhD; Donna M. Muzny, MS; Fan Xia, PhD; Zhiyv Niu, PhD; Richard Person, PhD; Yan Ding, MD; Patricia Ward, MS; Alicia Braxton, MS; Min Wang, PhD; Christian Buhay, BS; Narayanan Veeraraghavan, PhD; Alicia Hawes, BS; Theodore Chiang, MS; Magalie Leduc, PhD; Joke Beuten, PhD; Jing Zhang, PhD; Weimin He, PhD; Jennifer Scull, PhD; Alecia Willis, PhD; Megan Landsverk, PhD; William J. Craig, MD, PhD; Mir Reza Bekheirnia, MD; Asbjorg Stray-Pedersen, MD, PhD; Pengfei Liu, PhD; Shu Wen, PhD; Wendy Alcaraz, PhD; Hong Cui, PhD; Magdalena Walkiewicz, PhD; Jeffrey Reid, PhD; Matthew Bainbridge, PhD; Ankita Patel, PhD; Eric Boerwinkle, PhD; Arthur L. Beaudet, MD; James R. Lupski, MD, PhD; Sharon E. Plon, MD, PhD; Richard A. Gibbs, PhD; Christine M. Eng, MD
# Clinical Exome Sequencing Studies

<table>
<thead>
<tr>
<th></th>
<th>Baylor</th>
<th>UCLA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dates</strong></td>
<td>6/2012-11/2013</td>
<td>1/2012-9/2014</td>
</tr>
<tr>
<td><strong># of Cases</strong></td>
<td>2000</td>
<td>814</td>
</tr>
<tr>
<td><strong>Common Symptoms</strong></td>
<td>Predominantly neurologic (88%)</td>
<td>Children: Dev delay Adult: Ataxia</td>
</tr>
<tr>
<td><strong>Method</strong></td>
<td>Proband Exome</td>
<td>Proband Exome Trio Exome</td>
</tr>
<tr>
<td><strong>% Diagnosis</strong></td>
<td>25%</td>
<td>26%</td>
</tr>
</tbody>
</table>
Clinical Exome “Pearls”

• Dx rate varies by age, symptoms & method
• Many mutations de novo: 50% & 87%
• Dx often based on recent publications
• >90% of patients want “incidental” findings
• 3-5% of cases have incidental findings
• Insurance coverage similar to genetic tests
Genome results can identify inherited risks for disease to allow diagnosis, family member risk determination & targeted monitoring or prevention
Outline

- What is genomic medicine?
- Why use genomic medicine now?
- Genomic medicine applications
- Genomic medicine in Vermont
UVM Vision: Genomes for All
Genomic Medicine Program

Clinical Genomic Medicine

Biobank
- Genome Databank
- Healthcare Databank

Genomic Translational Research

Genomic Education
Genomic Medicine Program

Clinical Genomic Medicine

Biobank

Genome Databank

Healthcare Databank

Genomic Translational Research

Genomic Education
UVM Clinical Genomic Medicine Team

GENOMIC MEDICINE PROGRAM
Debra Leonard, MD, PhD, Director
Niki Sidiropoulos, MD, Medical Director
David Seward, MD, PhD, Attending
Ken Hampel, PhD
Courtney Scott, MT(ASCP)
Jordan Armstrong, MT

BIOINFORMATICS
PierianDx
Rakesh Nagarajan, MD, PhD
Julie Dragon, PhD

PARTNERS
Cardiology
Medical Genetics
OB/GYN
Oncology
Pathology
Patients
Pediatrics
Pharmacy
Radiology
Surgery
Everybody…
Genomic Medicine Tests

- Cancer gene panels (25-50 genes)
  - Solid tumor (29 genes) – LIVE as of 2/1/16
  - Hematologic malignancy (being validated; DNA & RNA)
  - Inherited cancer risk gene panel

- Pharmacogenomic gene panel (50-80 genes)

- Inherited disorders (exome or genome)
  - Specific multigene diseases (e.g. CV, NM disease)
  - Unidentified inherited disorder (e.g. NICU babies)
  - Over time, sequence genome of every person, if cost effective

Integrate Tests into Clinical Care Pathways
Genomic Care Pathways

- Clinical pathways to integrate genomic testing into patient care:
  - Identify patients who are appropriate for testing
  - Obtain informed consent
  - Obtain the right specimen
  - Perform genomic test & interpret in clinical context
  - Integrate genomic results into EHR
  - Discuss genomic results at multidisciplinary conferences
  - Counsel patient (& family), as appropriate
  - Test family members with informed consent, as indicated
Opening January 27, 2017!
Assess the value of each genomic test:
Are we improving patient outcomes?
Are we improving cost effectiveness?
Genomic Value Research: Data Collection

• For each new genomic test, collect data
  – Genomic results
  – Treatment
  – Response/outcomes
  – Total cost of care

• Data combined from multiple data sources
Genomic Value Research: Partnerships
Genomic Medicine Program

- Clinical Genomic Medicine
- Biobank
- Genome Databank
- Healthcare Databank
- Genomic Translational Research
- Genomic Education
Genomic Education

- Undergraduate education
- Medical student education
- Resident & Fellow Education
- Healthcare provider education

UVM Honors College: Controversies in Modern Genomics

Integrate Genetics & Genomic Medicine UVM COM Curriculum

Molecular Pathology Rotation

The University of Vermont
LARNER COLLEGE OF MEDICINE
THE UNIVERSITY OF VERMONT
HEALTH NETWORK
Purpose: Engagement to prepare for clinical genome sequencing

73 UVM members had genome sequenced
- Pre- & post-testing genetic counseling
- April 30, 2016: Symposium where got access to genome sequence on a web application

Research in collaboration with Harvard PeopleSeq Consortium (Robert C. Green)
Genomic Education

- Undergraduate education
- Medical student education
- Resident & Fellow Education
- Healthcare provider education
- Patient, family & public engagement & education

- UVM Honors College: Controversies in Modern Genomics
- Integrate Genetics & Genomic Medicine UVM COM Curriculum
- Molecular Pathology Rotation
- Understand Your Genome
Press, Community Talks, Focus Groups
Promise of Genomic Medicine

- Improve patient outcomes
- Improve population health, especially for families
- Improve cost-effectiveness of care

A Promising Future for Our Patients
Thank you!

Any questions?
The heart and science of medicine.