Making Genomic Medicine a Reality for Vermont

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Burlington, VT
Vermont is the Green Mountain State
“UVM” from Latin:
*Universitas Viridis Montis*
Outline

• The Setting
• My Vision in 2013
• Genomic Medicine Plan & Implementation
• The Future
Healthcare in Vermont
Vermont Population 626,011

Source: U.S. Census Bureau
Census 2000 Summary File 1
population by census tract.
Across Lake Champlain to NY
New York
Population
8.3 Million
2011 Green Mountain Care Law

- Improve the health of Vermonters
- Improve quality of healthcare
- Regulate healthcare costs:
  - Hospital budgets (<3.5% budget growth/year)
  - Major capital expenditures (CON process) and
  - Health insurance rates
- Approve plans:
  - For health insurance benefits in exchange program
  - To recruit and retain health professionals
- Build & maintain electronic health information systems
University of Vermont Health Network

UVM Medical Center
Porter Hospital
Central Vermont Medical Center
Alice Hyde Medical Center
Champlain Valley Physicians Hospital
Elizabethtown Hospital

Affiliation Agreement

2 FQHCs = Vermont Care Organization

OneCare Vermont

Adirondacks ACO
VERMONT ALL-PAYER ACCOUNTABLE CARE ORGANIZATION MODEL AGREEMENT

This Vermont All-Payer Accountable Care Organization ("ACO") Model Agreement ("Agreement") is dated October 27, 2016, and is between the Centers for Medicare & Medicaid Services ("CMS") and the Governor of Vermont, the Green Mountain Care Board ("GMCB"), and the Vermont Agency of Human Services ("AHS") (collectively, "State" or "Vermont"). Each Vermont entity, and CMS, is a party to the Agreement.

Percentage of Vermont Beneficiaries Aligned to an ACO.

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<tbody>
<tr>
<td>Vermont All-Payer Scale Target Beneficiaries</td>
<td>36%</td>
<td>50%</td>
<td>58%</td>
<td>62%</td>
<td>70%</td>
</tr>
<tr>
<td>Vermont Medicare Beneficiaries</td>
<td>60%</td>
<td>75%</td>
<td>79%</td>
<td>83%</td>
<td>90%</td>
</tr>
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All-payer Total Cost of Care per Beneficiary Growth Target.

\[
\left( \frac{\text{Vermont all-payer TCOC}_{2022}}{\text{Vermont all-payer beneficiaries}_{2022}} \right)^{\frac{1}{5}} - 1 \leq 0.035
\]

\[
\left( \frac{\text{Vermont all-payer TCOC}_{2017}}{\text{Vermont all-payer beneficiaries}_{2017}} \right)
\]
CENTERS FOR MEDICARE & MEDICAID SERVICES

Date 10/25/16
By: Amy Bassano
Amy Bassano, Deputy Director, Center for Medicare and Medicaid Innovation

GOVERNOR OF THE STATE OF VERMONT

Date 10/25/16
By: Peter Shumlin, Governor

GREEN MOUNTAIN CARE BOARD

Date 10/26/16
By: Al Gobeille, Chair, Green Mountain Care Board

VERMONT AGENCY OF HUMAN SERVICES

Date 10/27/16
By: Hal Cohen, Secretary, Vermont Agency of Human Services
Changing World View

Fee for Service

> Do = More $

Global Payment

< Do (IF keep people healthy) = More $

2017: 30% Medicaid is global payment in Vermont
Molecular Pathology in Vermont
Human Genome Project 2001
Sanger Capillary Electrophoresis Sequencing

Analog
Next Generation Sequencing 2004

Digital

$750K
Low Cost Next Gen Instruments Drove Clinical Genomics Forward

$75K-125K

✓ Gene Panels
× Exome

Next Generation Sequencing 2011
Clinical Genomic Medicine Programs in 2012

- **ARUP**: Large gene panel for *inflammatory bowel disease*
- **Emory**: X-linked *intellectual disability*
- **Illumina**: Exome analysis in CLIA lab for *constitutional* diagnosis
- **Johns Hopkins**: Cancer-specific rearrangements for cancer recurrence
- **MGH**: All lung *cancers* tested for 110 mutations in 13 genes
- **Partners Center for Personalized Genetic Medicine**: Large gene panels for cancer, cardiomyopathy, hearing loss, pharmacogenetics, connective tissue disorders, etc.
- **Vanderbilt**: All lung *cancers* and melanomas tested with 40 mutation panel
- **Washington University**: All *cancers* have complete sequence of 28 genes
- **Yale**: Exome sequencing for *congenital conditions* and cancer

**Focus on cancer & inherited disorders**

**Predominantly gene panels or exome**
Molecular/Genomics at UVMMC in 2012

• Extensive molecular/MS microbiology
• Genetics: FV, FII, MTHFR, HCR
• Cancer: JAK2
• Cytogenetics: Karyotyping, FISH

Barrier to Molecular Testing at UVMMC
Was Low Volume per Test
Reality for Molecular Pathology in Vermont

- Population: 626,011
- 35,500 Surgical & 32,000 Cytology
- 5.3M laboratory tests
- Test volume too low to develop
  - Cancer testing by tissue of origin
  - Inherited disorder testing by disease

Lower volumes common in much of US
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• The Future
Molecular Plan for Vermont was Genomics

- Skip molecular and use genomics
- Next gen for panels, exome, genome
- Limited number of genomic tests
- Each test used for many patients
- Use molecular methods for validations & confirmations
UVM Vision: Genomes for All
Genotype Drives Phenotype

Genotype: red°/red° red°/red° red°/red° red°/Y red°/Y

Phenotype: ♀ ♀ ♀ ♀ ♂ ♀
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*
Genome results may identify disease risks before onset of symptoms
  – Targeted monitoring only for at risk individuals
  – Preventive strategies, when available
Exome/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
- Ehlers–Danlos syndrome, vascular type
- Marfan syndrome, Loeys–Dietz syndromes, and familial thoracic aortic aneurysms and dissections
- Hypertrophic cardiomyopathy, dilated cardiomyopathy, and 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

**56 Genes for 23 Diseases with Evidence for Clinical Utility**

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

Genome

Epigenome

Environment

YOU

Medical Phenotype

Healthcare Provider (EHR)

Patient
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*
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Genomic Medicine Program

Clinical Genomic Medicine

Biobank
Genome Databank
Healthcare Databank

Genomic Translational Research

Genomic Education
Clinical Genomic Medicine Plan for next 3 to 5 years
Genomic Medicine Clinical 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

*Integrating 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
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
Margaret Cameron

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

Partners
Cardiology
Medical Genetics
OB/GYN
Oncology
Pathology
Patients
Pediatrics
Pharmacy
Radiology
Surgery
Everybody...
# Building the Genomic Medicine Team

<table>
<thead>
<tr>
<th>Year</th>
<th>People</th>
<th>Progress</th>
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| 2013 | Debra Leonard, MD, PhD  
       Niki Sidiropoulos, MD  
       Courtney Scott, MT(ASCP) | 5-Yr Business Plan  
PierianDX License Decision & Work Purchasing |
| 2014 | Ken Hampel, PhD | 5-Yr Business Plan Approval  
IT & Test Method Design/Validation |
| 2015 | Jordan Armstrong  
Pre-authorization staff | Redo Business Plan and Lab Design (CON)  
Negotiations with payers  
Gene Panel Solid Tumor Test Validation |
| 2016 | David Seward, MD, PhD  
Margaret Cameron | Gene Panel Solid Tumor Test Live (DNA)  
Solid Tumor RNASeq Validation  
Start Genomic Oncology TDT |
| 2017 | Robert Wildin, MD  
Genetic Counselor | Reflex unresectable CRC, Lung & Melanomas  
Hemepath Gene Panel Design & Validation |
Collaboration for Interpretation

• Human Genome Project Center
• Began clinical genomics 3 years ago
• 12 faculty
• 35 bioinformatics
• 6 medical informatics staff

http://cancer.sanger.ac.uk/cancergenome/projects/census/
Clinical Genomicist Workstation: Workflow

1. **Patient**
   - Physician
     - Sample
       - Order
         - Sequence
           - Tier 1: Base Calling, Alignment, Variant Calling
             - Genome Annotation
               - Tier 2: Medical Knowledgebase
                   - EHR
                     - Tier 3: Clinical Genomicist Workstation
Genomic Oncology Trans Disciplinary Team

• Chaired by Niki Sidiropoulos
• Participants from
  – Pathology
  – Oncology
  – Radiation Oncology
  – Basic Scientists from UVM Cancer Center
• Meet every other week
• Discuss cases & plan research
Assess the value of each genomic test:  
Are we improving patient outcomes?  
Are we improving cost effectiveness?
• 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

[Logos and images of individuals and organizations]
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
UVM Understand Your Genome Program

• 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)
• Nine (12.3%) with hereditary risk for clotting
  – Six with Factor V Leiden Thrombophilia
  – Three with Prothrombin-Related Thrombophilia
• Six (8.2%) with Familial Periodic Fever (*TNFRSF1A*)
• Six (8.2%) with Mannose-Binding Protein Deficiency
  – Two homozygous & four compound heterozygous (*MBL2*)
• Four (5.4%) with Hereditary Hemochromatosis (*HFE*)
  – Two homozygous & two compound heterozygous
  – Penetrance very low
Three (4.1%) with pathogenic variants
- One *BRCA1* variant
- One *BRCA2* variant
- One *MYBPC3* variant

Breast Cancer
Hypertrophic Cardiomyopathy
UVM UYG: Carrier Status

- 9 Alpha-1 Antitrypsin Deficiency (12.3%)
- 7 Glycogen Storage Disease, Type II (9.5%)
- 6 Cystic Fibrosis (8.2%)
- 1 Phenylalanine hydroxylase deficiency (PKU)
- 1 Congenital Disorder of Glycosylation, Type IIb
- 1 Joubert syndrome
UVM UYG: PGx for 4 Most Common Drugs

- Clopidogrel
- Simvastatin
- Tricyclic antidepressants
- Warfarin Metabolism
- Warfarin Sensitivity
UVM UYG: PGx for 4 Most Common Drugs

- Factor V Leiden
- Prothrombin-related thrombophilia

8/9 People with Clotting Risk Need Different Warfarin Dosing

1 3 5 7 9 11 13 15 25 27 29 31 33 35 37 39 41 43 45 47 49 51 53 55 57 59 61 63 65 67 69 71 73

- ticagrelor
- clopidogrel
- Simvastatin
- Tricyclic antidepressants
- Warfarin Metabolism
- Warfarin Sensitivity
Genomic Education

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

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Integrate Genetics & Genomic Medicine UVM COM Curriculum
Molecular Pathology Rotation
Understand Your Genome
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• The Setting
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• Continue clinical & education work
• Focus on genomic implementation science

Robert Wildin, MD
Chief, Genomic Healthcare Branch, NHGRI
Joining UVM August 7, 2017
The Future

• Keep with the clinical & education plans
• Focus on genomic implementation science
• Increase PFCC engagement for genomes
• Decide if genomes next after cancer tests
• Increase external grant funding
• Integrate genomics into MS3 & MS4 years
• Consider value of Center or Institute status
The 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 for the Invitation