The heart and science of medicine.

Genomic Medicine in Vermont

Debra G.B. Leonard, M.D., Ph.D.
Chair & Professor
Department of Pathology & Laboratory Medicine
UVM College of Medicine& UVM Health Network
Burlington, VT

The University of Vermont
LARNER COLLEGE OF MEDICINE

THE University of Vermont
HEALTH NETWORK

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

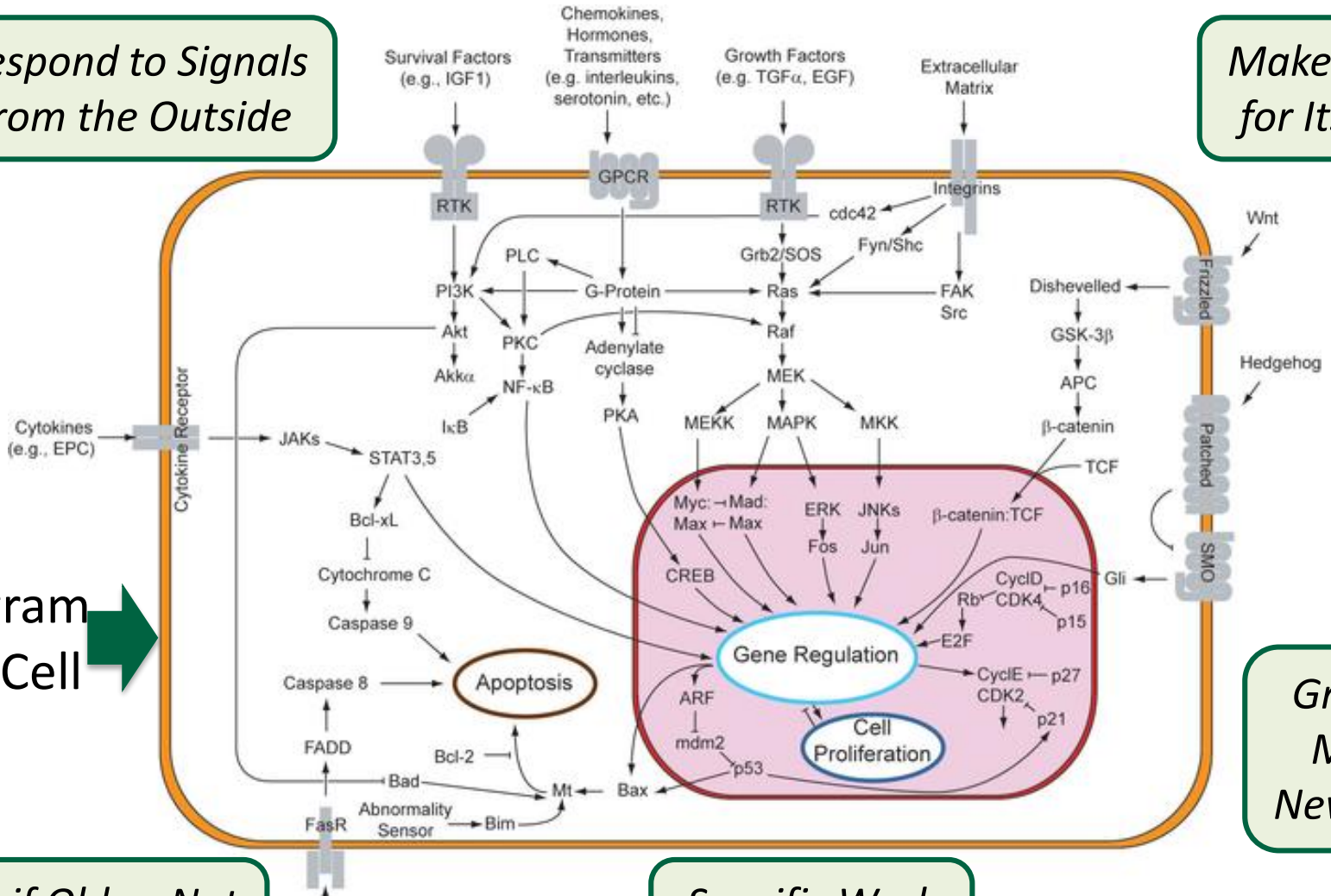
- What is genomic medicine?
- Why use genomic medicine now?
- Genomic medicine applications
- Genomic medicine in Vermont

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

Diagram of a Cell



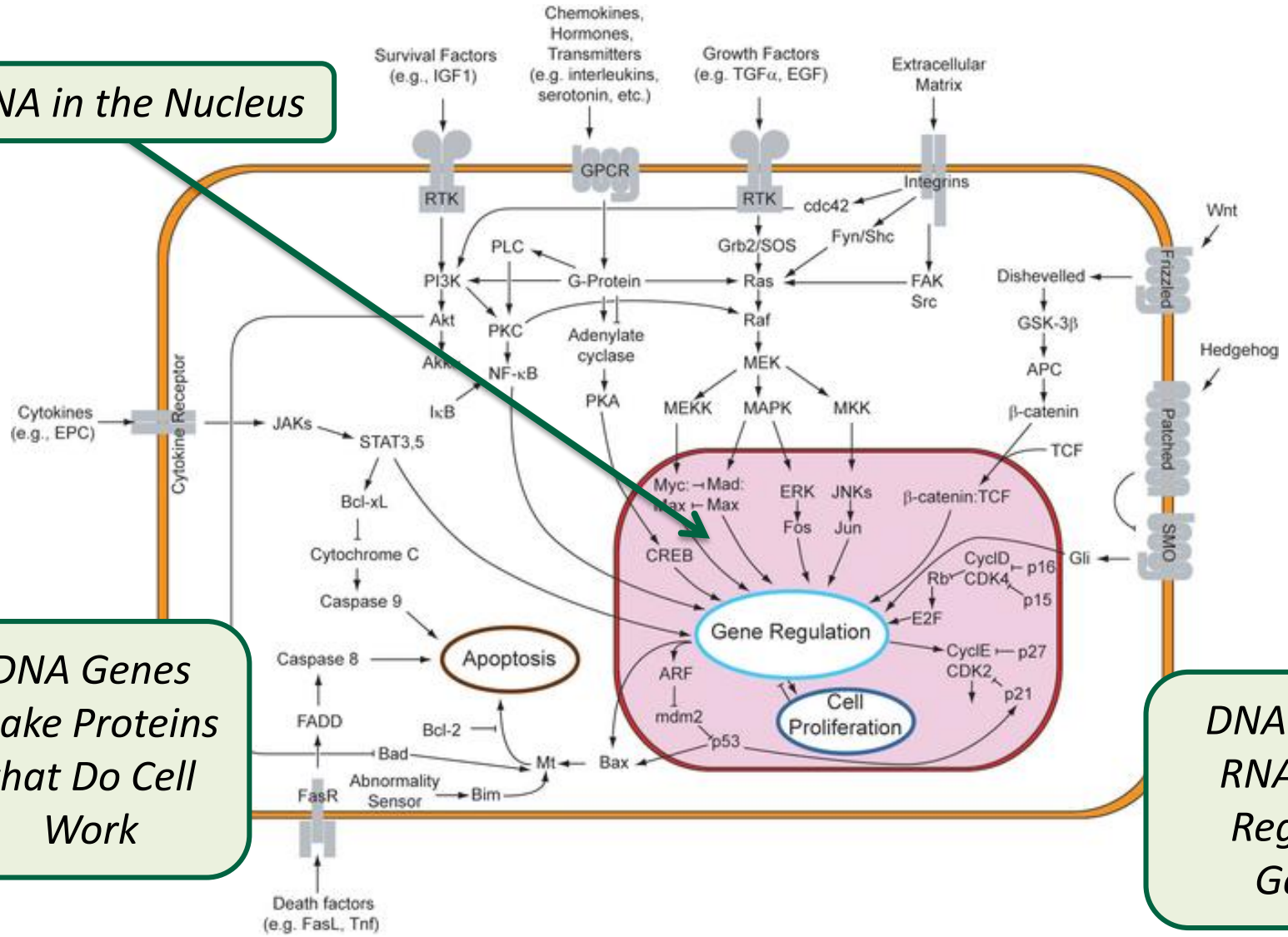
Grow & Make New Cells

Die if Old or Not Working Right

Specific Work of the Cell

DNA Directs the Cell Work

DNA in the Nucleus

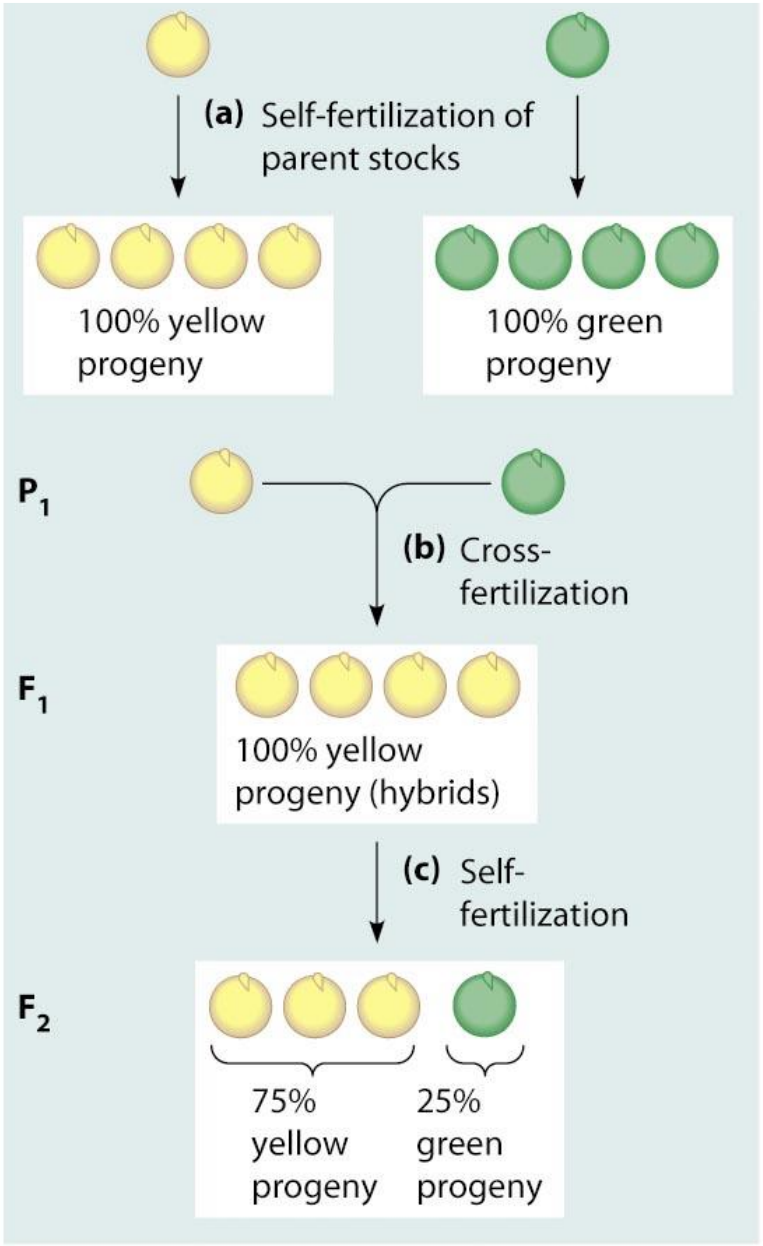


DNA Genes Make Proteins that Do Cell Work

DNA Makes RNAs that Regulate Genes

Gregor Johann Mendel (1822 – 1884)

PHENOTYPE
(What We See)



PHENOTYPE: Blue Eyes

Brown Eyes

GENOTYPE: bb

Recessive: b

BB or Bb

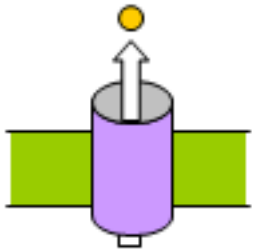
Dominant: B

Physical Features

GENOTYPE

PHENOTYPE

***CFTR* Gene (DNA)**



CFTR wild type protein
ion transport normal

→ **Healthy**

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

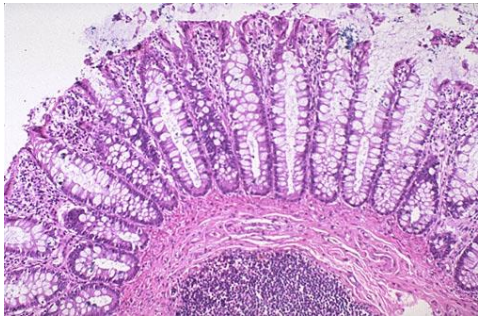
Winston Churchill

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

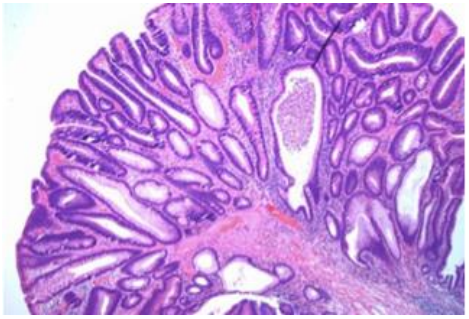
Multifactorial Common Diseases

Cancer Genomics

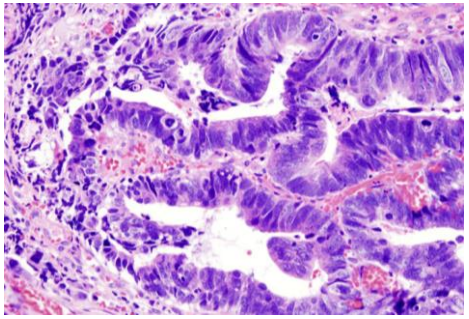
Normal



Adenoma



Cancer



Leading Causes of Death in U.S.

Heart Disease	596,577
Cancer	576,691
Chronic Lung Disease	142,943
Stroke	128,932
Accidents	126,438
Alzheimer Disease	84,974
Diabetes	73,831
Influenza & Pneumonia	53,826
Kidney Disease	45,591
Suicide	39,518

All Influenced By Genomic Variation

CDC: National Vital Statistics Report 2011

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

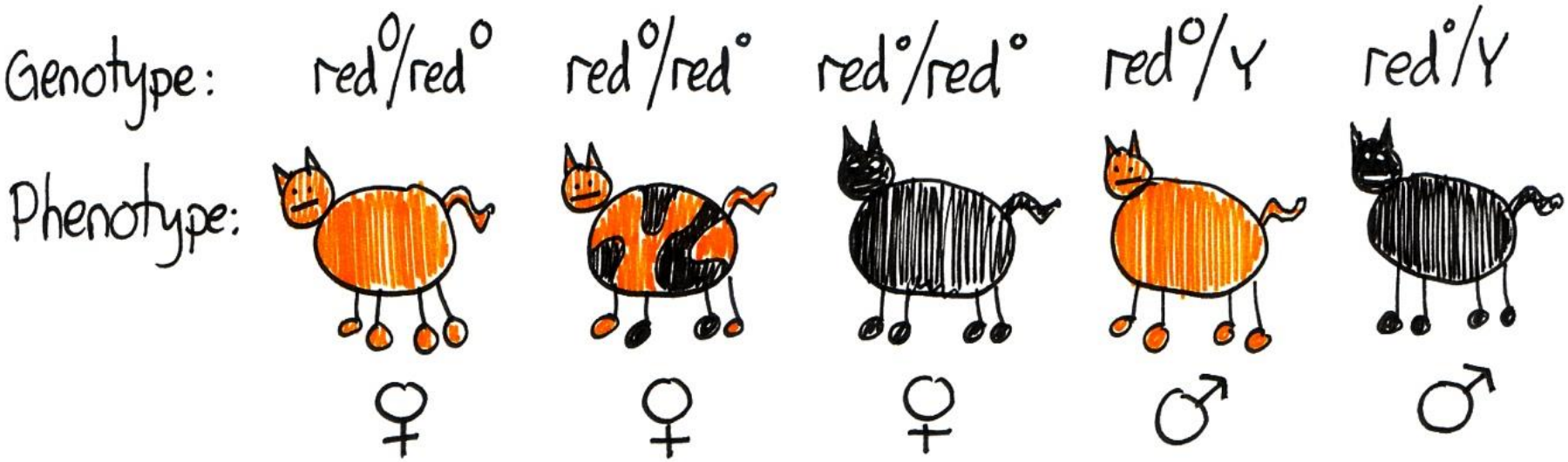
Precision Medicine

Personalized Medicine

Outline

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

Genotype Drives Phenotype



A Genome contains Fundamental Medical Information


FAMILIES
6065

SOUTH

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

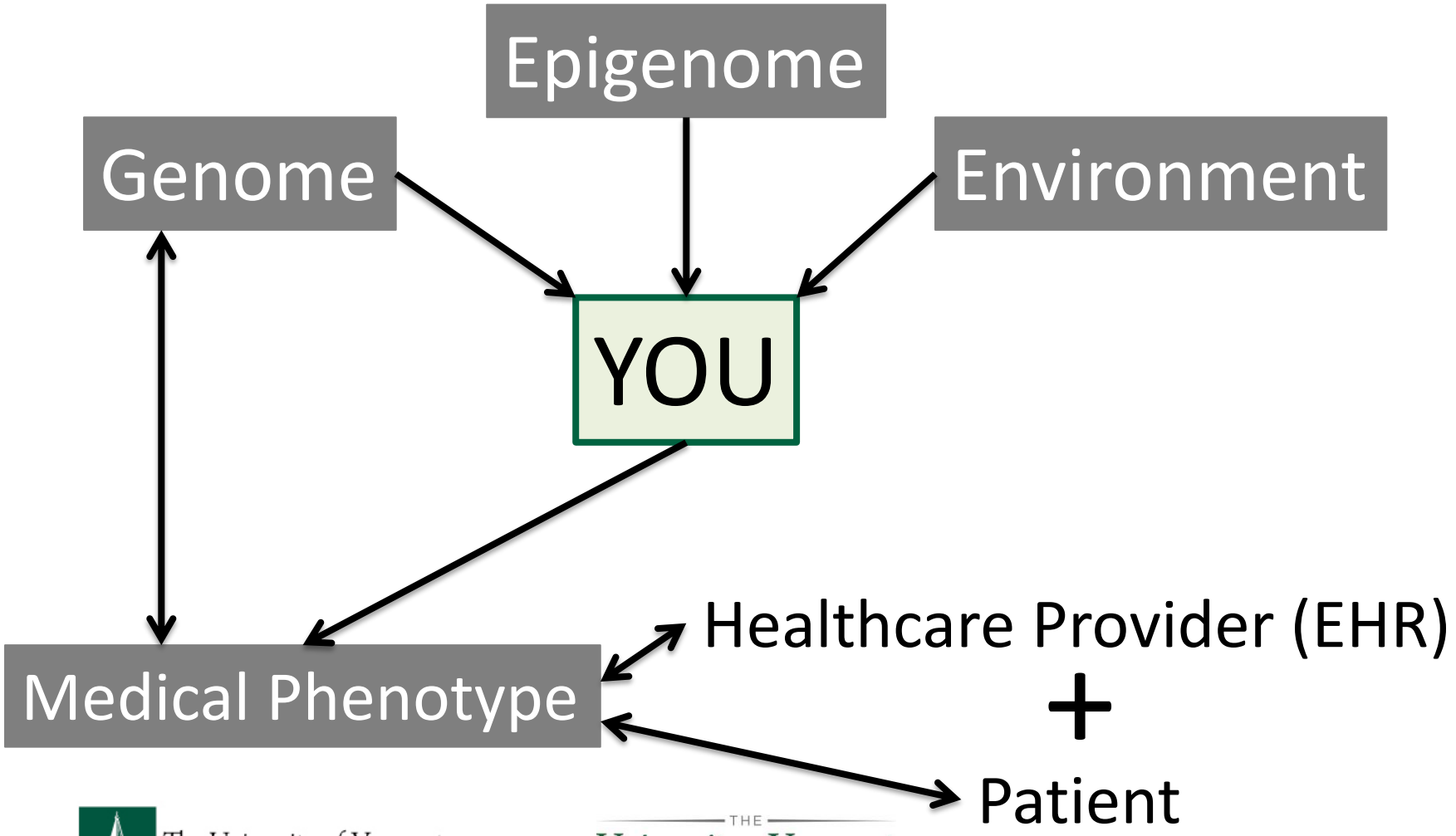
Genome Reportable Results (ACMG)

- 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
- Familial medullary thyroid
- *PTEN* hamartom ome
- Retinob
- H paraganglioma-ph chromocytoma syndrome
- Tuberous sclerosis complex
- *WT1*-related Wilms tumor
- Neurofibromatosis type 2
- Ehlers–Danlos syndrome, vascular type
- Marfan syndrome, Loeys–Dietz syndromes, and familial th rtic aneurysms and diss
- Hypertroph athy, dilated card
- aminergic polymorphic entricular 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



The University of Vermont
LARNER COLLEGE OF MEDICINE

THE University of Vermont HEALTH NETWORK

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?
- Why use genomic medicine now?
- Genomic medicine applications
- 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

Home ▾ | Resources ▾ | Curation ▾ | Tools ▾ | Data ▾ | News ▾ | Help ▾ | About ▾ | Search COSMIC... | Login ▾

Census | Breakdown | Abbreviations

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.

Show 100 entries Export: CSV TSV Search:

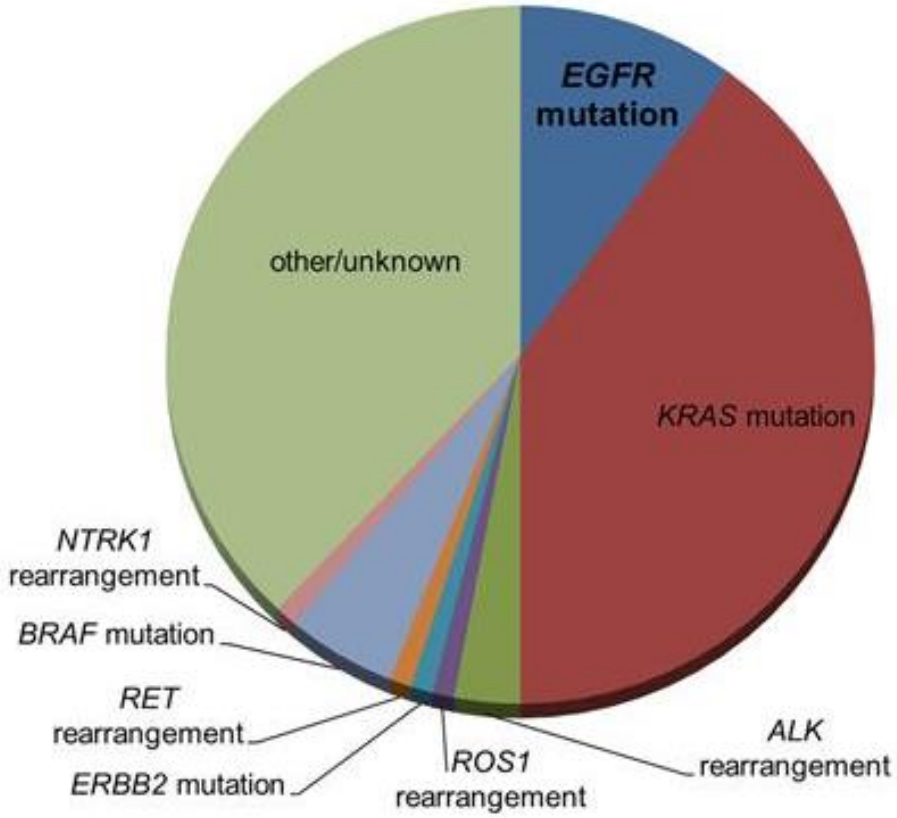
Gene Symbol	Name	Entrez GeneId	Genome Location	Chr Band	Somatic	Germline	Tumour Types(Somatic)
ABI1	abl-interactor 1	10006	10:26748570-26860863	10p11.2	yes		AML
ABL1	v-abl Abelson murine leukemia viral oncogene homolog 1	25	9:130835447-130885683	9q34.1	yes		CML; ALL; T-ALL
ABL2	c-abl oncogene 2; non-receptor tyrosine kinase	27	1:179107718-179143044	1q24-q25	yes		AML
ACKR3	atypical chemokine receptor 3	57007	2:-	2q37.3	yes		lipoma

http://cancer.sanger.ac.uk/cancergenome/projects/census/

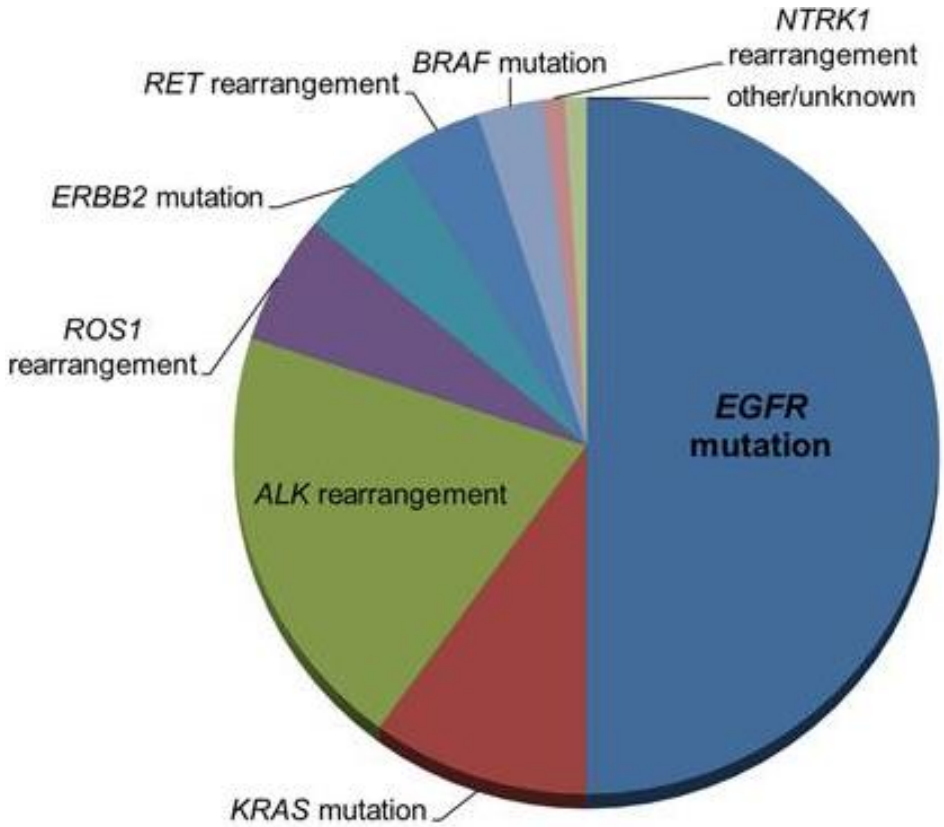
Lung Cancer Driver Mutations

Non-small cell lung cancer, adenocarcinoma

Smokers

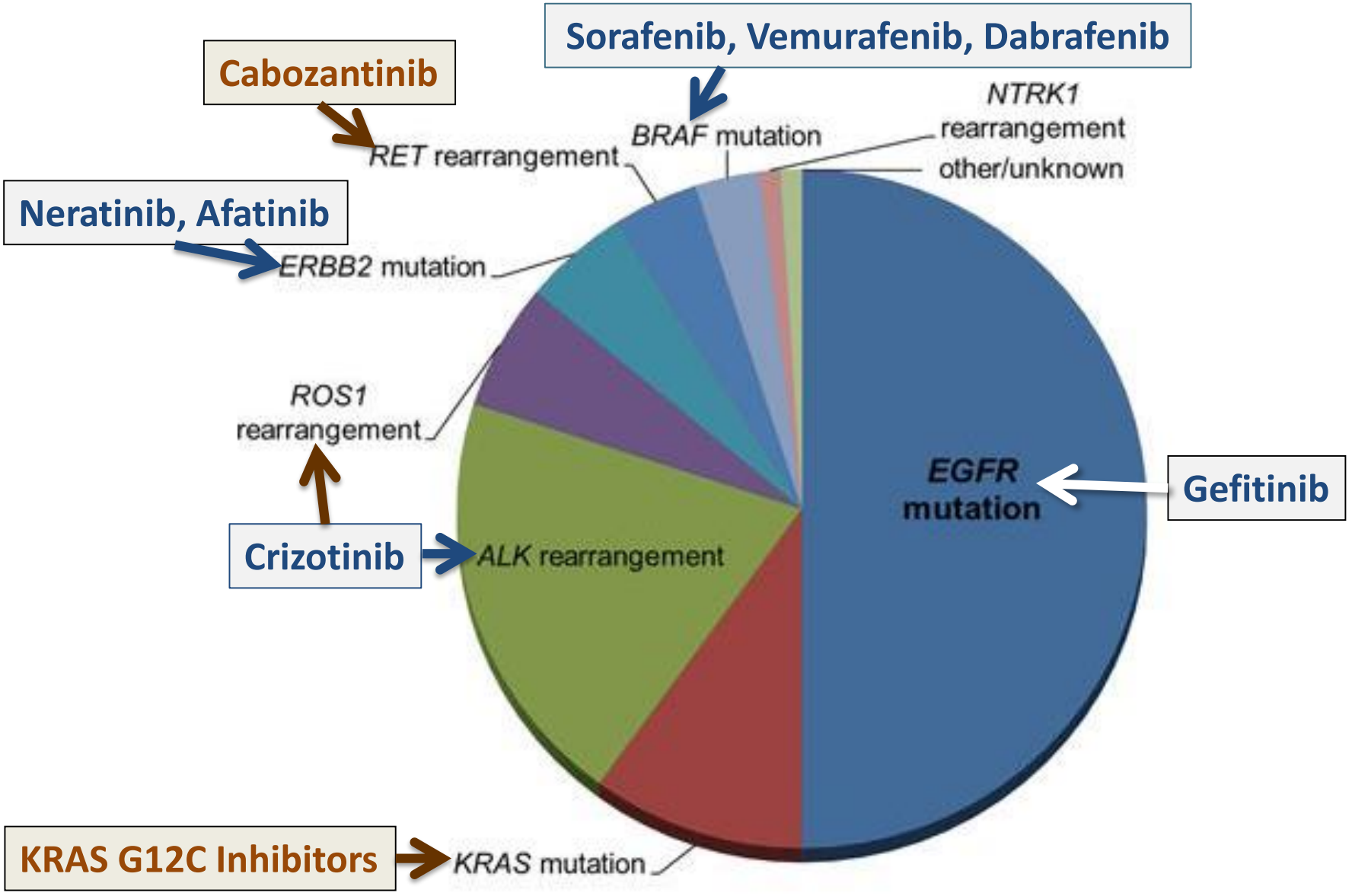


Non-Smokers



Braz J Med Biol Res vol.47 no.11 Ribeirão Preto Nov. 2014 Epub Sep 05, 2014

Lung Cancer Driver Mutations: Non-Smokers



Braz J Med Biol Res vol.47 no.11 Ribeirão Preto Nov. 2014 Epub Sep 05, 2014

Research Original Investigation

JAMA. 2014;311(19):1998-2006. doi:10.1001/jama.2014.3741

Using Multiplexed Assays of Oncogenic Drivers in Lung Cancers to Select Targeted Drugs

Mark G. Kris, MD; Bruce E. Johnson, MD; Lynne D. Berry, PhD; David J. Kwiatkowski, MD; A. John Iafrate, MD; Ignacio I. Wistuba, MD; Marileila Varella-Garcia, PhD; Wilbur A. Franklin, MD; Samuel L. Aronson, ALM, MA; Pei-Fang Su, PhD; Yu Shyr, PhD; D. Ross Camidge, MD, PhD; Lecia V. Sequist, MD; Bonnie S. Glisson, MD; Fadlo R. Khuri, MD; Edward B. Garon, MD; William Pao, MD, PhD; Charles Rudin, MD, PhD; Joan Schiller, MD; Eric B. Haura, MD; Mark Socinski, MD; Keisuke Shirai, MD; Heidi Chen, PhD; Giuseppe Giaccone, MD; Marc Ladanyi, MD; Kelly Kugler, BA; John D. Minna, MD; Paul A. Bunn, MD

1007 Tumors Tested for at least 1 Gene
733 Tumors Tested for 10 Genes
466 with Oncogenic Driver (64%)

	Mutation AND Targeted Therapy	Mutation BUT NOT Targeted Therapy
Number of Patients	260	318
Median Survival	3.5 Years	2.4 Years

$P = 0.006$

Use of genome-directed treatments for cancer results in better outcomes with fewer side effects

The University of Vermont
LARNER COLLEGE OF MEDICINE

THE
University of Vermont
HEALTH NETWORK

Genomic Medicine Applications

- Cancer Genomics
- Pharmacogenomics
- Inherited Disorders

Pharmacogenomics (PGx)

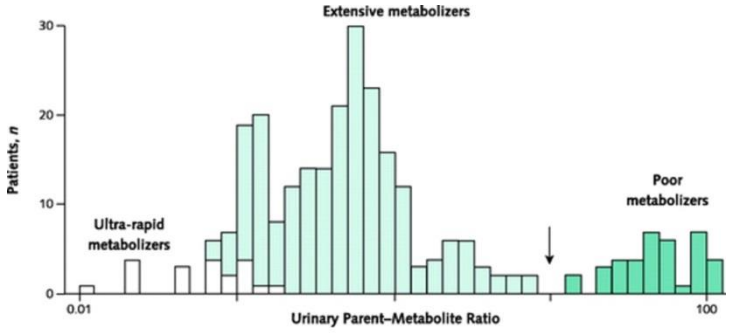
Genetic variations can change:

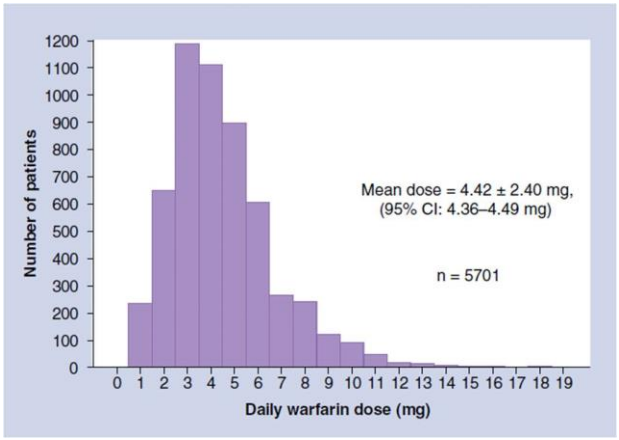
- Drug metabolism (activation/inactivation)
- Drug transport (absorption, distribution, excretion)
- Drug action (variation in drug target)

Evans W, McLeod HL. NEJM 2003;348:538-549

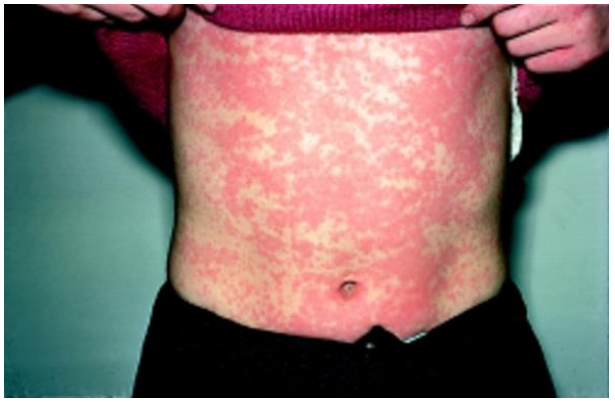
Two Goals of Pharmacogenomics

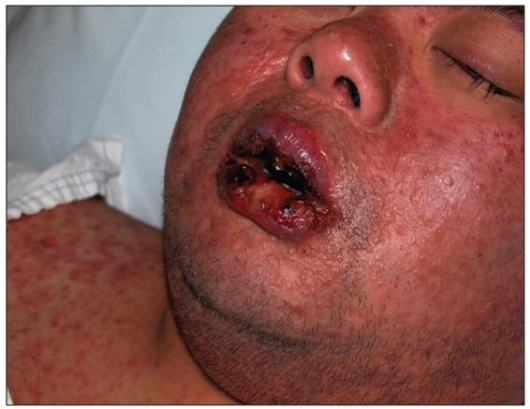
1. Achieve Effective Dosing





2. Avoid Adverse Drug Reactions





The University of Vermont
LARNER COLLEGE OF MEDICINE

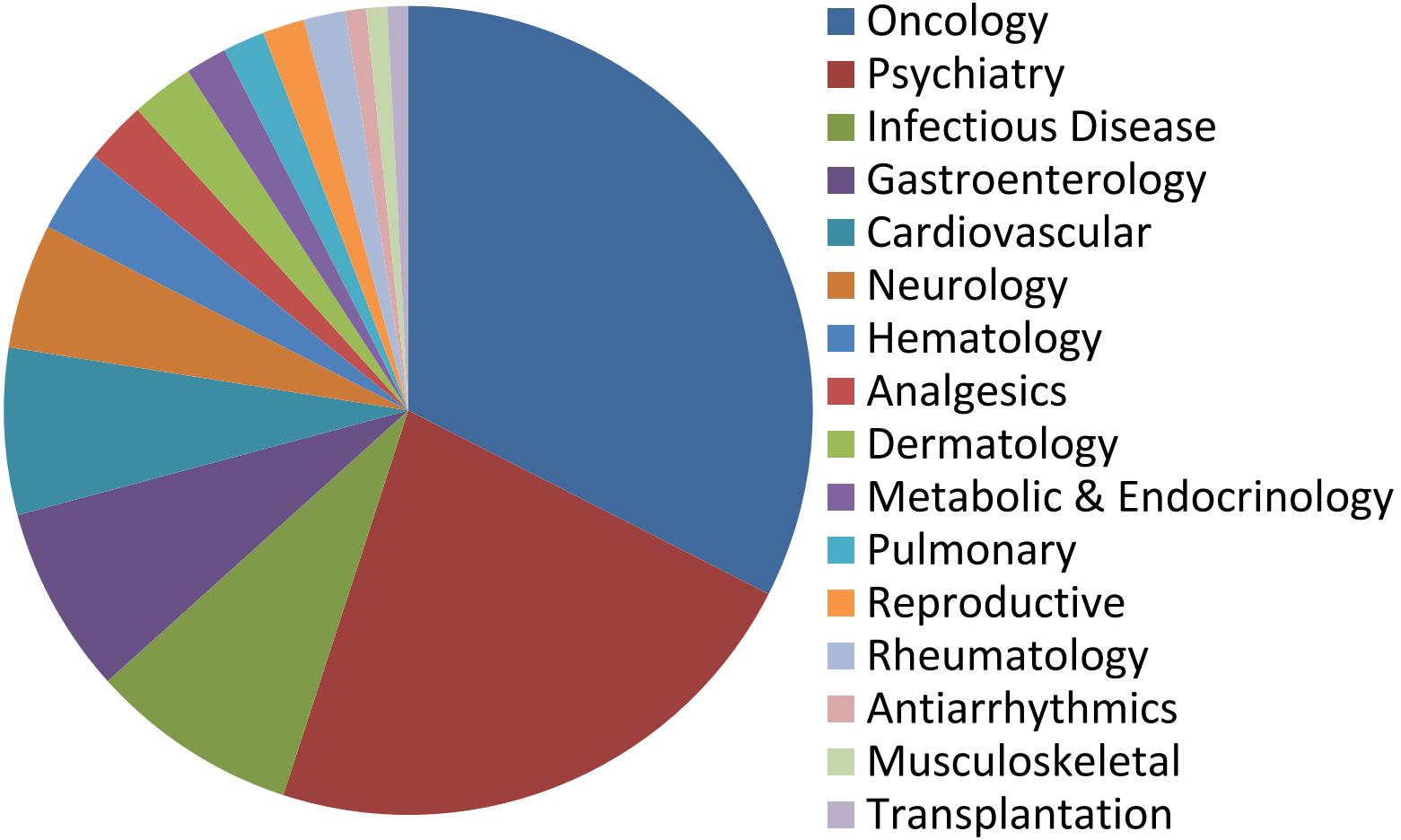
THE University of Vermont HEALTH NETWORK

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

CPIC: Implementing PGx
a PharmGKB & PGRN collaboration

PGx dosing guidelines available for 32 medications

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

http://www.pharmgkb.org/view/dosing-guidelines.do?source=CPIC

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

The University of Vermont
LARNER COLLEGE OF MEDICINE

THE University of Vermont HEALTH NETWORK

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 Hospi
- 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

69 Genes Related to Arrhythmias & Cardiomyopathies

Cardiovascular Disease	Genes
Long QT Syndrome	*AKAP9, ANK2, CACNA1C, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNJ5, KCNQ1, SCN4B, SCN5A, SNTA1*
Brugada Syndrome	*CACNA1C, CACNB2, GPD1L, HCN4, KCND3, KCNE3, KCNJ8, SCN1B, SCN3B, SCN5A*
Catecholaminergic Polymorphic Ventricular Tachycardia	*ANK2, CALM1, CASQ2, KCNJ2, RYR2*
Short QT Syndrome	*CACNA1C, CACNB2, KCNH2, KCNJ2, KCNQ1*
Hypertrophic Cardiomyopathy	*ACTC1, ACTN2, CSRP3, GLA, LAMP2, MYBPC3, MYH6, MYH7, MYL2, MYL3, MYLK2, MYOZ2, NEXN, PLN, PRKAG2, TNNC1, TNNI3, TNNT2, TPM1, TTR*
Dilated Cardiomyopathy	*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*
Left Ventricular Non-compaction Cardiomyopathy	*ACTC1, CASQ2, DTNA, LDB3, LMNA, MYBPC3, MYH7, TAZ, TNNT2, VCL*
Arrhythmogenic Right Ventricular Cardiomyopathy	*DES, DSC2, DSG2, DSP, JUP, PKP2, RYR2, TMEM43*

Two Inherited Disorder Applications

- Specific Multigene Diseases (e.g. Inherited Cardiovascular Disease)
- Unidentified Inherited Disorders

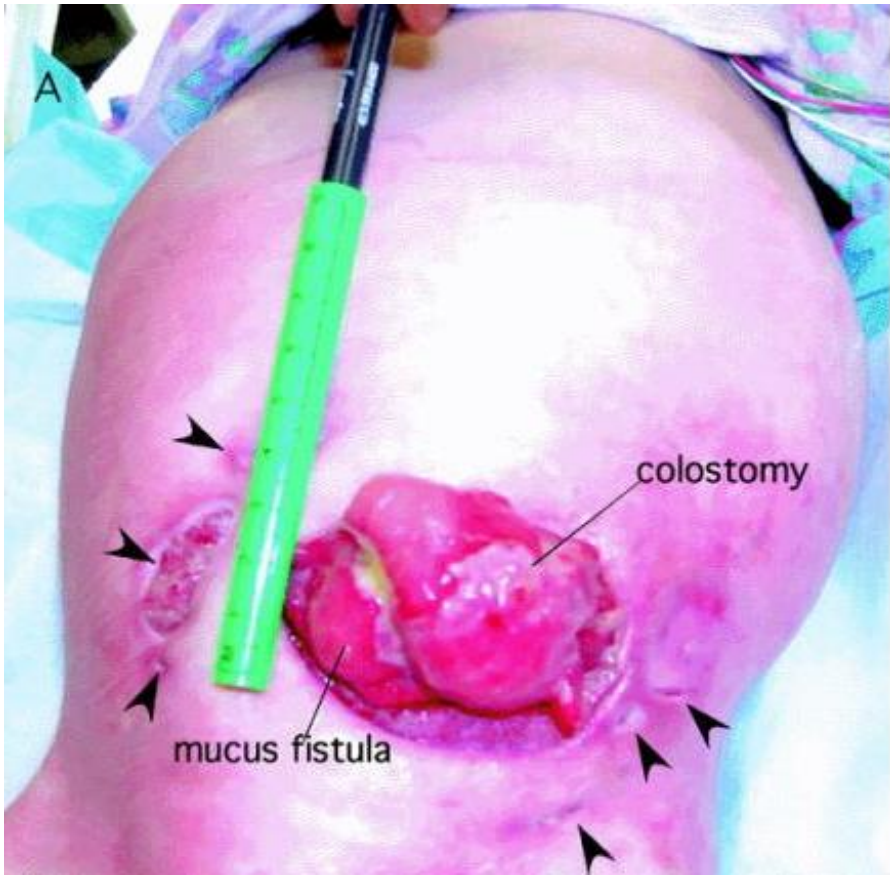
Child with Intractable IBD

- 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

Genetics in Medicine. 13(3):255-262, 2011.

Child with Intractable IBD - 2

- At 30 months old, sigmoid colostomy performed & long term total perenteral nutrition started
- Within 6 wks, developed bacterial sepsis



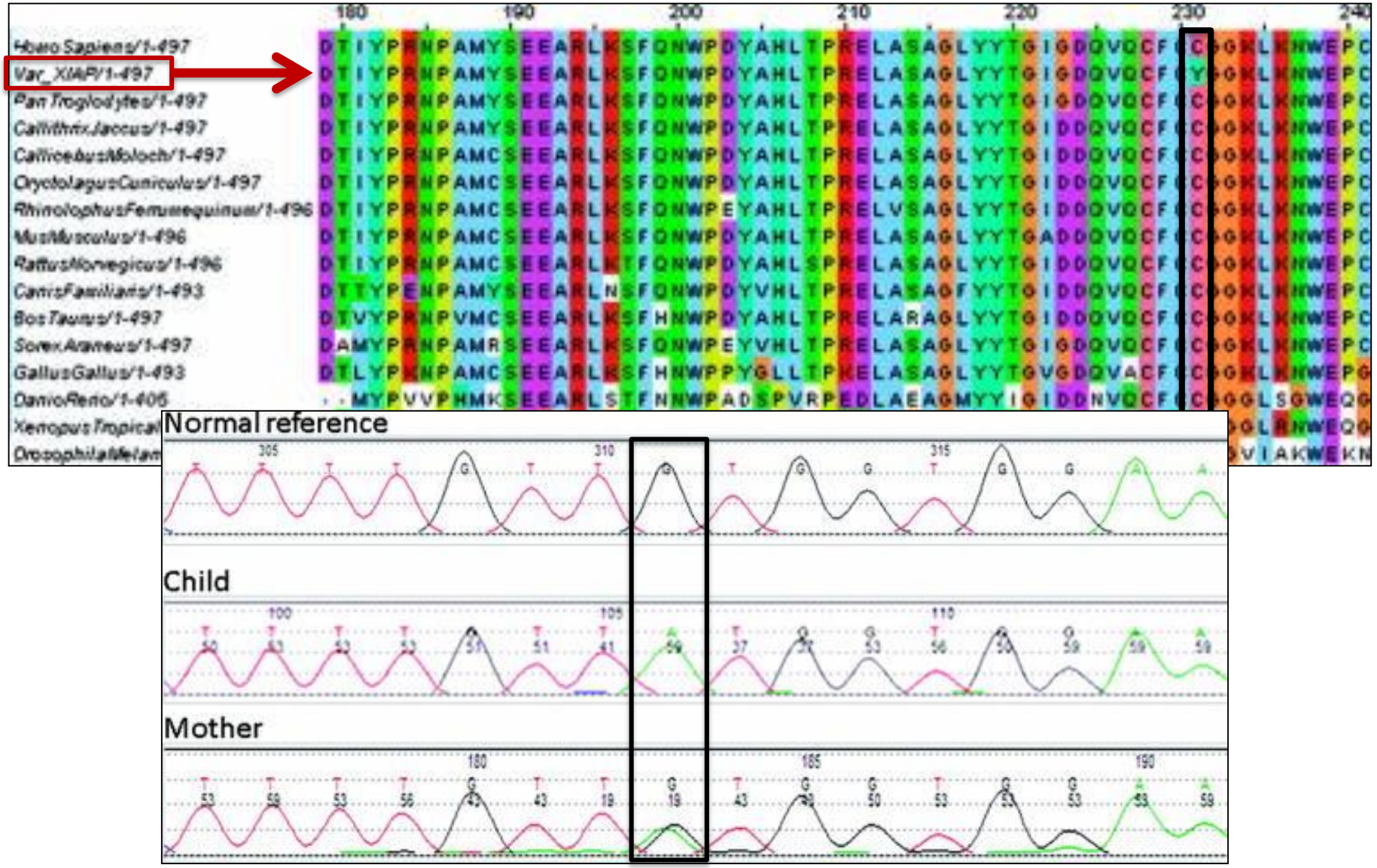
Genetics in Medicine. 13(3):255-262, 2011.

Child with Intractable IBD - 3

- 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

Genetics in Medicine. 13(3):255-262, 2011.

XIAP Mutation (X Chromosome)



Genetics in Medicine. 13(3):255-262, 2011.

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

Genetics in Medicine. 13(3):255-262, 2011.

Original Investigation

Clinical Exome Sequencing for Genetic Identification of Rare Mendelian Disorders

JAMA. 2014;312(18):1880-1887. doi:10.1001/jama.2014.14604
Published online October 18, 2014.

UCLA

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

Original Investigation

Molecular Findings Among Patients Referred for Clinical Whole-Exome Sequencing

JAMA. 2014;312(18):1870-1879. doi:10.1001/jama.2014.14601
Published online October 18, 2014.

Baylor

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. Craigen, 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

	Baylor	UCLA
Dates	6/2012-11/2013	1/2012-9/2014
# of Cases	2000	814
Common Symptoms	Predominantly neurologic (88%)	Children: Dev delay Adult: Ataxia
Method	Proband Exome	Proband Exome Trio Exome
% Diagnosis	25%	26%

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

The University of Vermont
LARNER COLLEGE OF MEDICINE

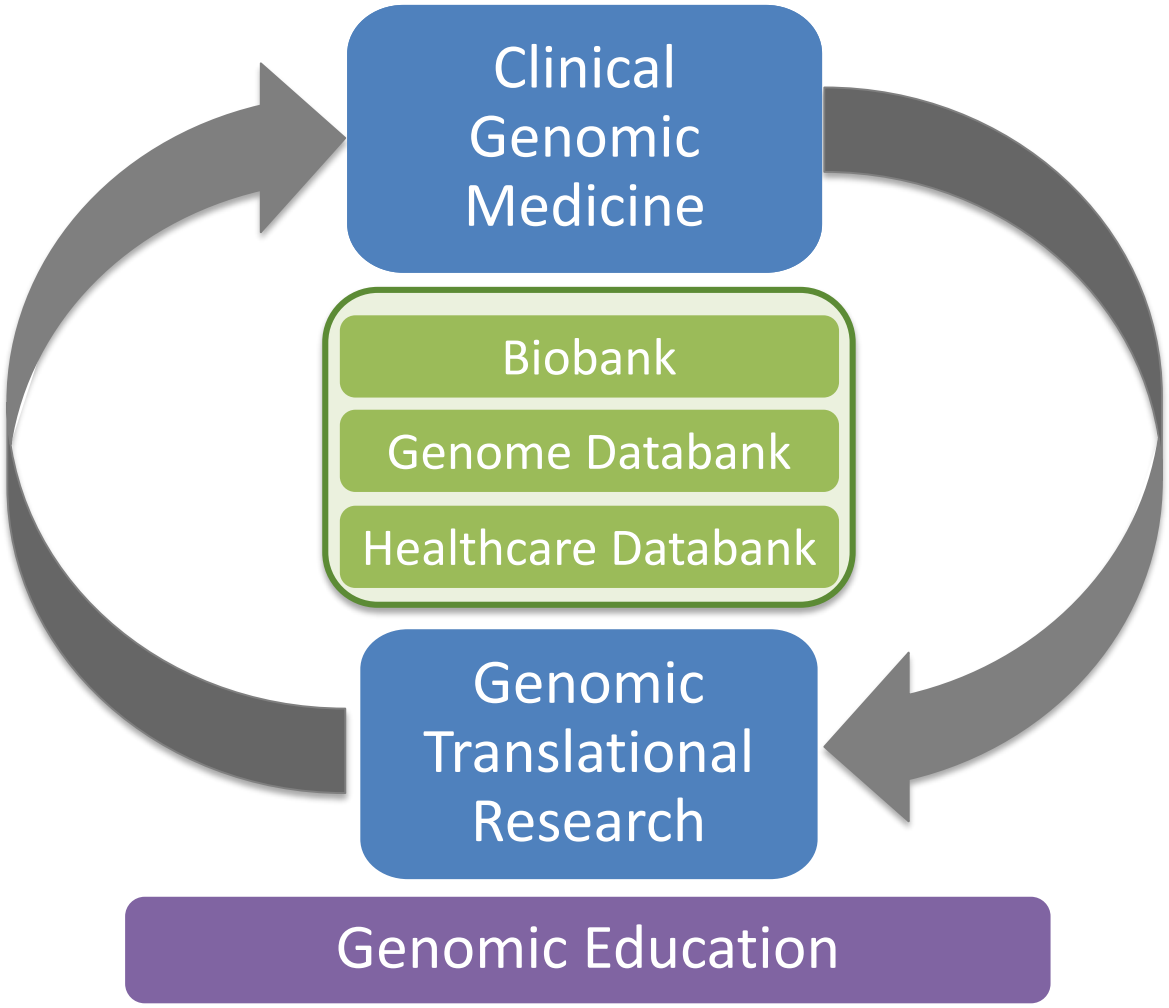
THE University of Vermont HEALTH NETWORK

Outline

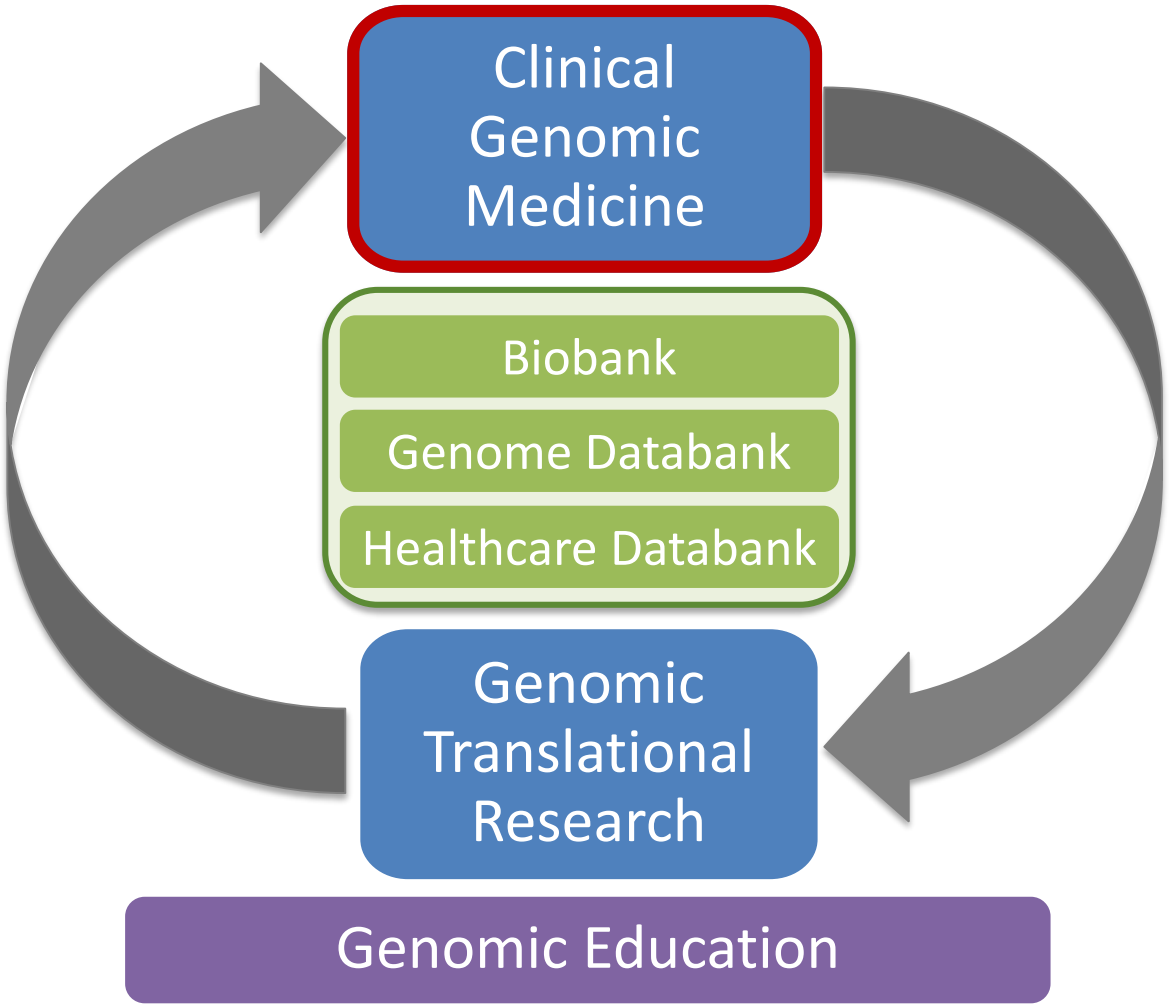
- What is genomic medicine?
- Why use genomic medicine now?
- Genomic medicine applications
- Genomic medicine in Vermont

UVM Vision: Genomes for All

Genomic Medicine Program



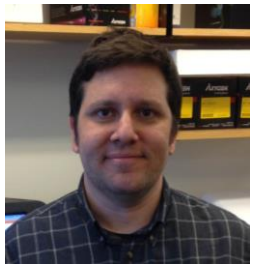
Genomic Medicine Program

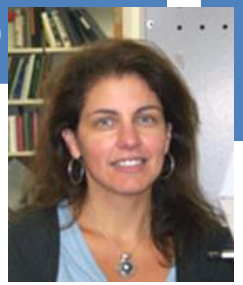


The University of Vermont
LARNER COLLEGE OF MEDICINE

THE University of Vermont HEALTH NETWORK

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

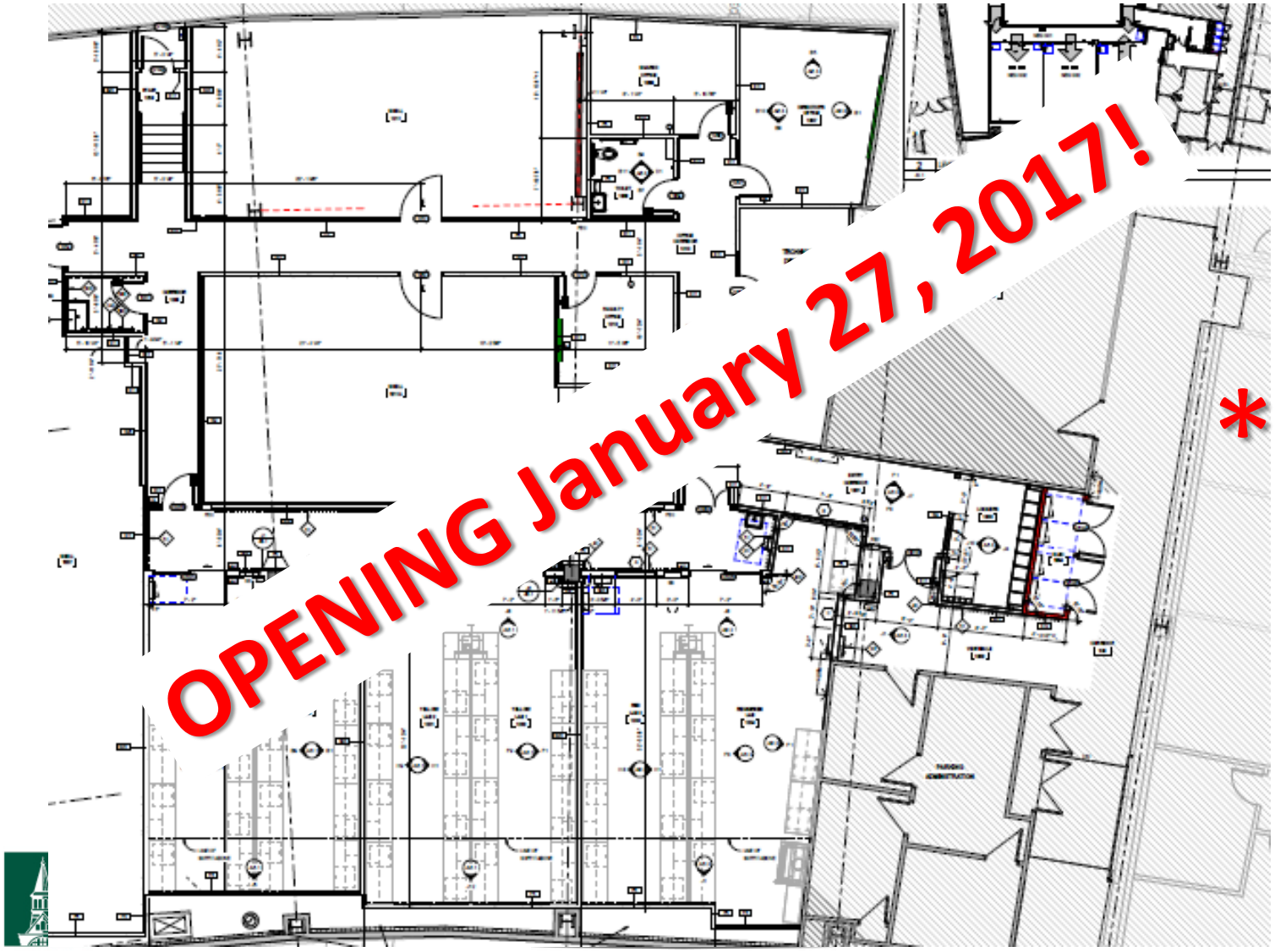
- Cancer gene panels (25-50 genes)
  - Solid tumor (29 genes) – LIVE as of 2/1/16
  - Hematologic malignancy (being validated; DNA & RNA)
  - Inherited cancer risk gene panel
- Pharmacogenomic gene panel (50-80 genes)
- Inherited disorders (exome or genome)
  - Specific multigene diseases (e.g. CV, NM disease)
  - Unidentified inherited disorder (e.g. NICU babies)
  - Over time, sequence genome of every person, if cost effective

Integrate Tests into Clinical Care Pathways

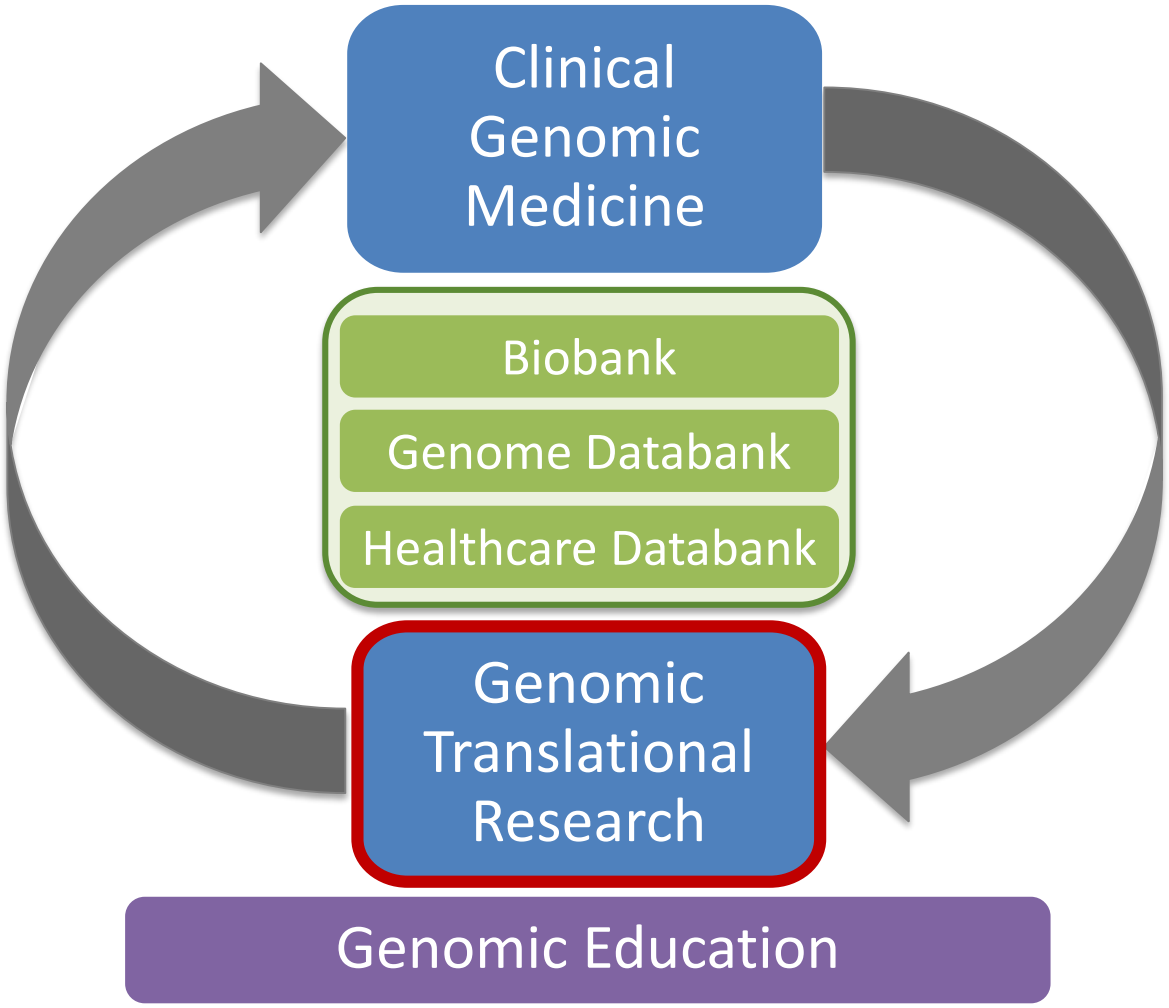
Genomic Care Pathways

- 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

New Genomic Medicine Laboratory



Genomic Medicine Program



Assess the value of each genomic test:

Are we improving patient outcomes?

Are we improving cost effectiveness?

The University of Vermont
LARNER COLLEGE OF MEDICINE

THE University of Vermont HEALTH NETWORK

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

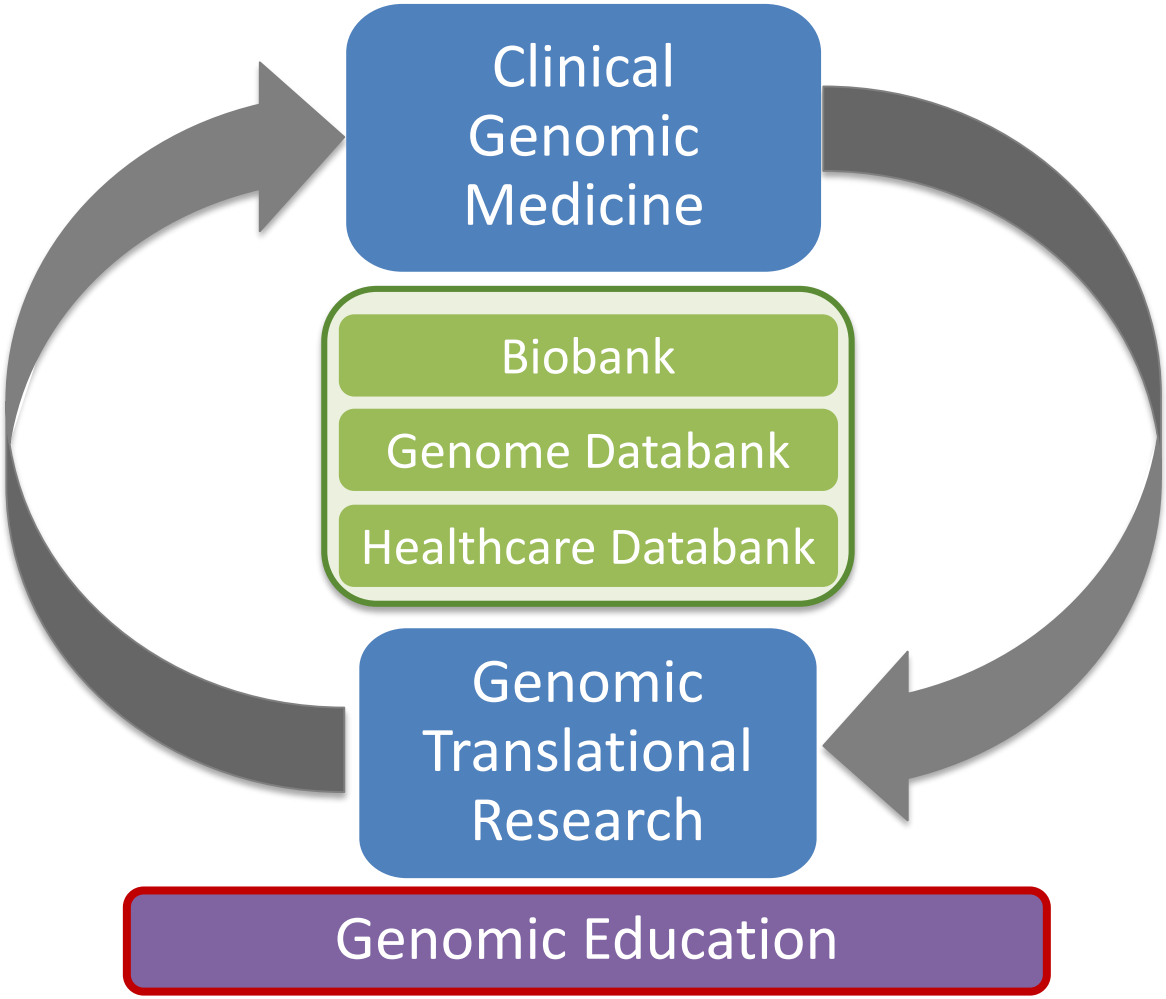
THE University of Vermont HEALTH NETWORK

PierianDx
enabling personalized medicine

PRECISION HEALTH ECONOMICS
PART OF PRECISION FOR VALUE

GENOSPACE

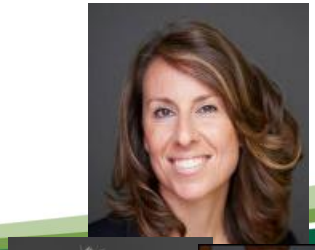
Genomic Medicine Program

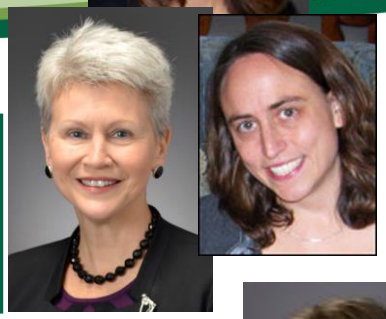


The University of Vermont
LARNER COLLEGE OF MEDICINE

THE University of Vermont HEALTH NETWORK

Genomic Education



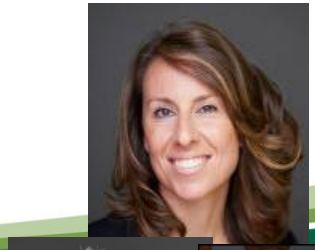


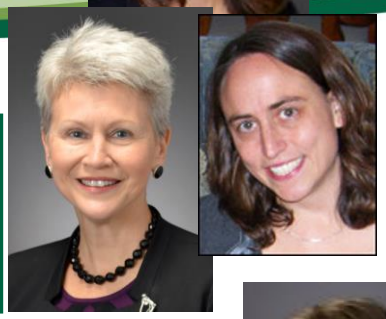
- Undergraduate education → UVM Honors College: Controversies in Modern Genomics
- Medical student education → Integrate Genetics & Genomic Medicine UVM COM Curriculum
- Resident & Fellow Education → Molecular Pathology Rotation
- Healthcare provider education → illumina® Understand Your Genome

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)

Genomic Education





- Undergraduate education → UVM Honors College: Controversies in Modern Genomics
- Medical student education → Integrate Genetics & Genomic Medicine UVM COM Curriculum
- Resident & Fellow Education → Molecular Pathology Rotation
- Healthcare provider education → illumina® Understand Your Genome
- Patient, family & public engagement & education

The University of Vermont LARNER COLLEGE OF MEDICINE

THE University of Vermont HEALTH NETWORK

Press, Community Talks, Focus Groups

Burlington Free Press
SUNDAY 06.05.16
PART OF THE USA TODAY NETWORK

MEDICINE'S FUTURE

University of Vermont Medical Center blazes trail to map patients' genetic makeup and avert disease. Story by Dan D'Ambrosio, 2A

Learning about genes at UVM Medical Center

Posted: Apr 30, 2016 6:06 PM EDT
Updated: May 02, 2016 6:06 PM EDT

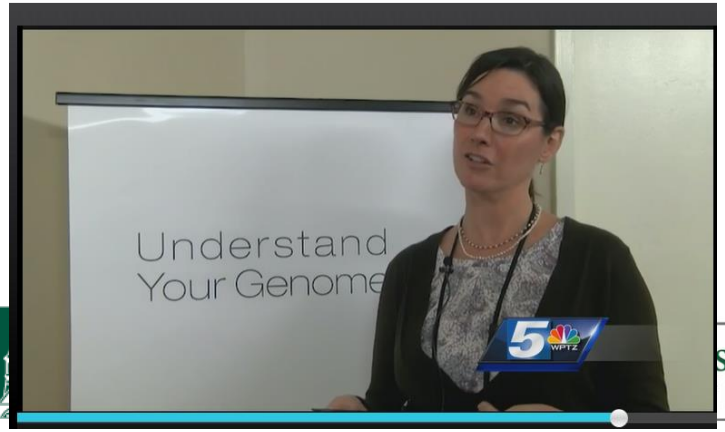
By Rose Spillman CONNECT

WCAX.com

UVM Medical Center closer to personalized medicine

UPDATED 11:40 AM EDT May 02, 2016

WPTZ.com NEWS CHANNEL 5



VPR Vermont's NPR News Source

For One Vermont Man, Sequencing His Whole Genome Solved A Life Of Pain

By KATHLEEN MASTERSON • MAY 12, 2016

SHARE
Twitter
Facebook
Google+
Email

For Greg Merhar, deciding to have his whole genome sequenced ended up diagnosing the cause of pain he'd lived with his whole life. His wife, Dr. Debra Leonard, recently spearheaded a pilot study at UVM to sequence the genomes of 73 university staff.

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 University of Vermont
LARNER COLLEGE OF MEDICINE

THE University of Vermont HEALTH NETWORK