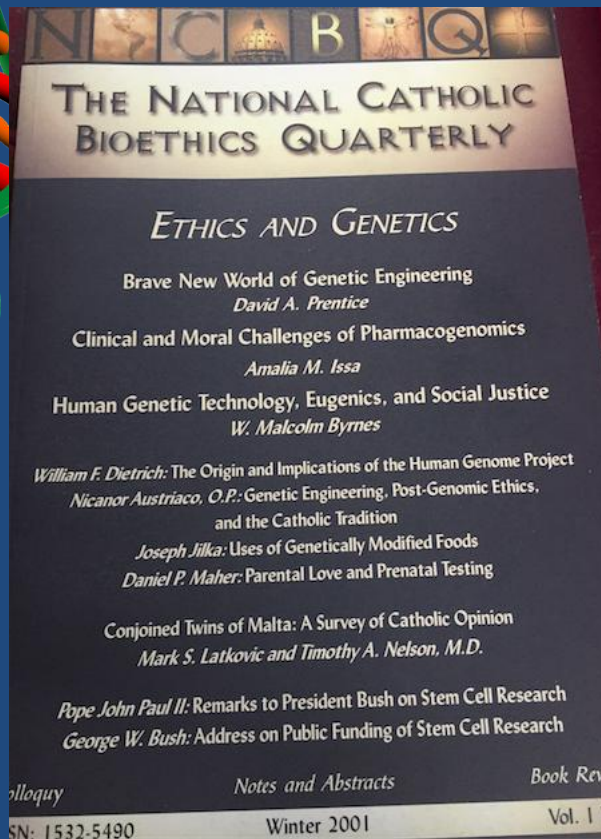


# Ethics and Personalized Medicine

Amalia M. Issa, PhD, MPH, FCP  
Professor and Founding Head  
Personalized Medicine & Targeted Therapeutics  
Professor of Pharmaceutical Sciences  
Professor of Health Policy & Public Health



## Clinical and Moral Challenges of Pharmacogenomics

Amalia M. Issa

With the landmark developments from the Human Genome Project (HGP), we have now entered the era of genomic drug discovery and development. The terms pharmacogenetics and pharmacogenomics are often used interchangeably to describe the study of genetic variations that underlie the differences in drug responsiveness between individuals. Traditionally, pharmacogenetics was considered the study of genetic factors that underlie the differences among people and populations in their ability to metabolically clear drugs.<sup>1</sup> The more recently coined term, "pharmacogenomics" is more encompassing, describing the impact of genomic information on the drug discovery process. Therefore, pharmacogenomics includes identifying target genes and genetic polymorphisms (genetic variations leading to differences in response to a medication), correlation of these polymorphisms with therapies, pre-

## Ethical considerations in clinical pharmacogenomics research

Amalia M. Issa

In recent years there have been unprecedented advances in our understanding of the involvement of genetic polymorphisms in the response to drug therapies. Polymorphisms have been identified that lead to variable patient responses to several medications including cardiovascular, psychiatric, anti-infective and analgesic therapies. The potential for the development of customized, genotype-based therapies is scientifically and clinically attractive. However, these developments, although bearing scientific promise, raise ethical concerns for the conduct of research with human subjects, particularly with respect to confidentiality, risk-benefit analysis, DNA-banking and pharmacoeconomic issues. This article discusses some of the ethical considerations that are related to the use of pharmacogenomics in clinical research protocols.

## ETHICAL PERSPECTIVES ON PHARMACOGENOMIC PROFILING IN THE DRUG DEVELOPMENT PROCESS

Amalia M. Issa

Pharmacogenomics, which is a field that encompasses the study of genetic polymorphisms that underlie individual differences in drug response, is rapidly advancing. The potential for the widespread use of pharmacogenomics in the drug development process merits an examination of its fundamental impact on clinical-trial design and practice. This article provides a critical analysis of some of the issues that pertain to pharmacogenomics in the drug development process. In

Trends in Pharmacol Sci. 2001

Nature Rev Drug Discov 2002



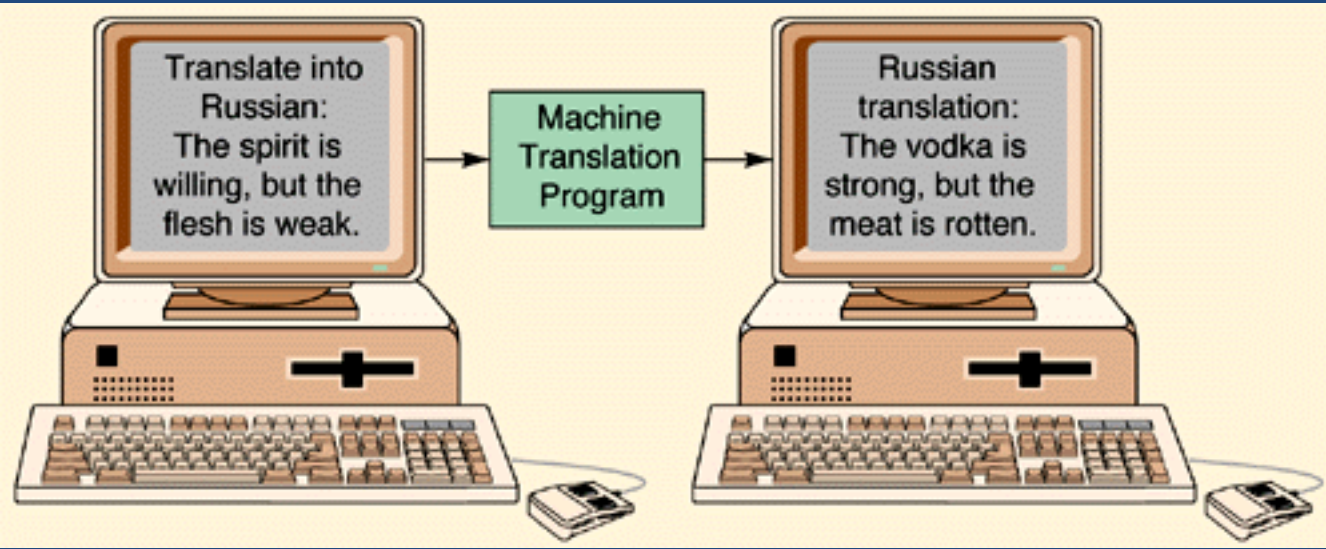
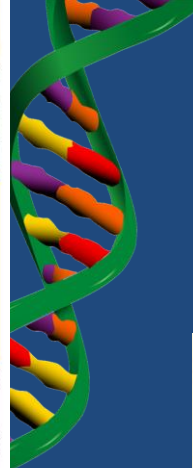




Rx



Dx



PhD in Neuroscience (neuropharm)  
from McGill University



MPH, UCLA SPH



Some theological and Catholic  
ethics training at Regis College, U  
of Toronto



Fellowships, Harvard Medical School







The Washington Post

Workblog

Hot dogs, bacon and other processed meats cause cancer, World Health Organization

# Testicles Of Yogurt-Eating Mice Shown Bigger, And Researchers Credit Probiotics

Elle 'in

Last summer a team of researchers from the Massachusetts Institute of Technology set out to better understand the effects of yogurt on

## Tall women have higher cancer risk; are smoking, drinking to blame?

July 25, 2013 | By Monte Morin

Email

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Recommend 0

The taller a postmenopausal woman is, the greater risk she faces of developing cancer, according to a new study.

In a paper published Thursday in the journal Cancer Epidemiology, Biomarkers & Prevention, researchers concluded that a woman's cancer risk increased 13% with every 4 inches of height.

The study is the latest of several to report an association between women's height and cancer, according to lead study author Geoffrey Kabat, a cancer epidemiologist at Albert Einstein College of Medicine in New York.

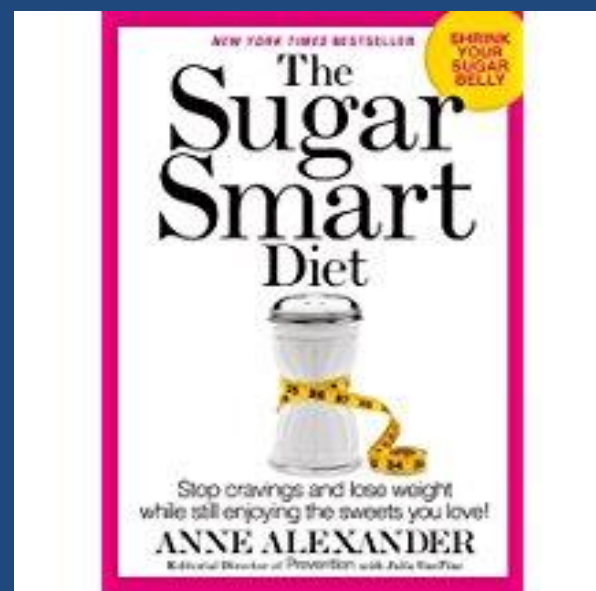
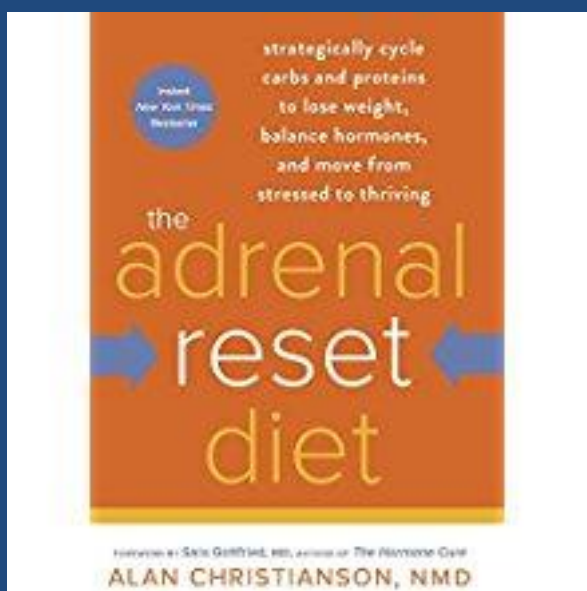
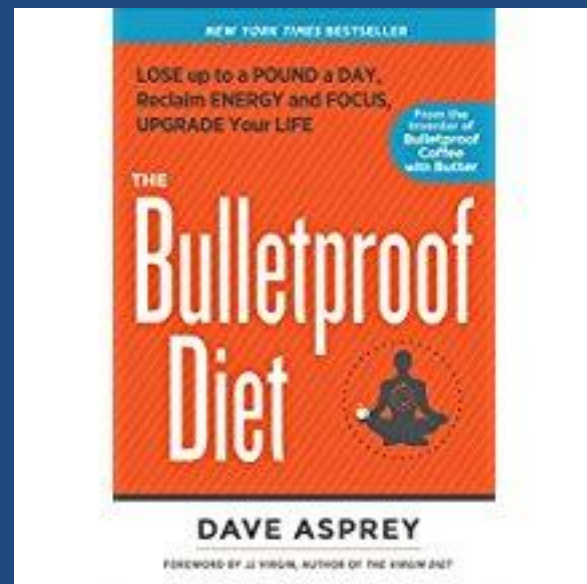
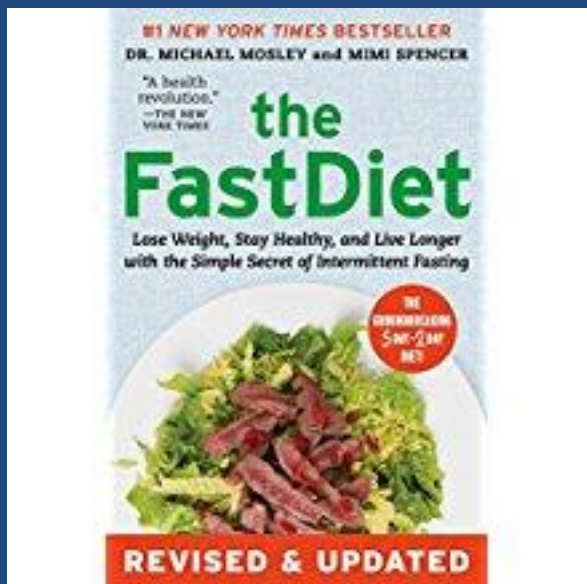
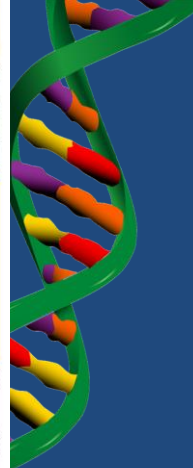


A new study has linked women's height to cancer risk. (Divyakant Solanki / European...)



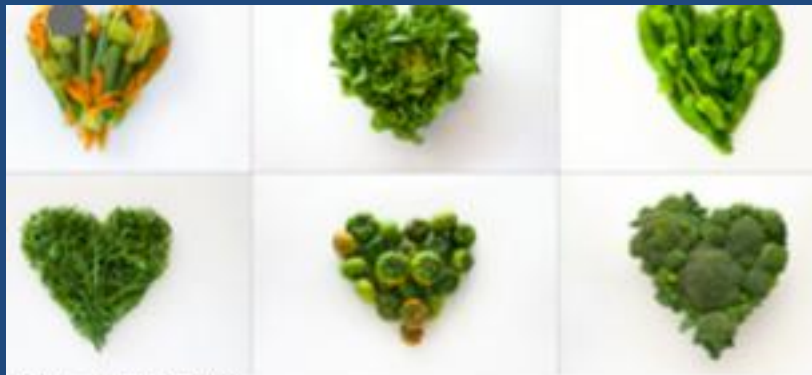
# Museum Tour

- Good ethics begins with good science
- Autonomy & Privacy/Confidentiality
- Issues related to Big Data
- How the Church Can Contribute to the Dialogue





# Green Foods May Power Your Cells Like Plants



PATRIZIA SAVARESE VIA GETTY IMAGES

How many times have you heard the recommendation to eat your greens? Kale, bok choy, mustard greens, broccoli and other vegetables have been praised as superfoods and are often rated as the healthiest foods to eat. Although there are many components of these foods that contribute to health like the fiber, minerals, micronutrients and antioxidants, the green color itself may aid our health. Why are these vegetables green? And how does that help our health?

They are green because they contain large amounts of chlorophyll. Chlorophyll is from the Latin "green leaf" and is the green color leaves and plants. Chlorophyll is formed in the cells of the leaves and other parts of the plants exposed to light. Green plants take in sunlight and transform it into energy. This is called photosynthesis. Chlorophyll is

Huffington Post,  
5/23/2016



Good ethics begins with good science.

THERE is no good science without good judgment  
and no good judgment without good ethics

# *Era of Precision Medicine has Arrived*

No commonly agreed upon definition of the term  
“Personalized Medicine”



Widely understood that *personalized medicine* refers to:

A medical model using characterization of individuals' ***phenotypes*** (observable physical and biochemical characteristics) and ***genotypes*** (e.g. molecular profiling) along with medical imaging, lifestyle data for tailoring the right therapeutic strategy and/or to deliver timely and targeted prevention.





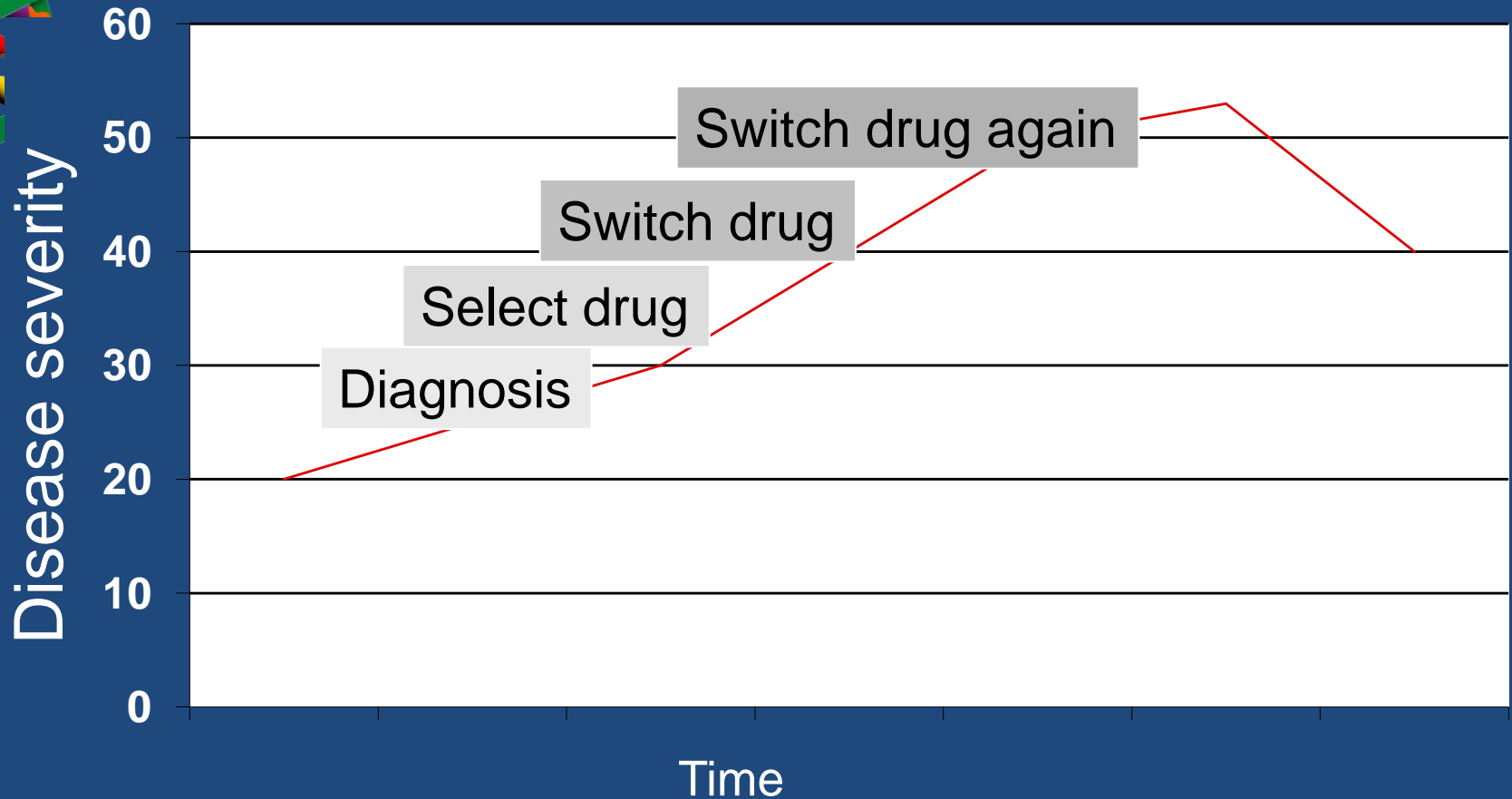
# From personalized medicine to precision medicine

Precision medicine implies that diseases are defined by underlying molecular mechanisms rather than traditional signs and symptoms.

*Lancet 378 : 1678, 2011*

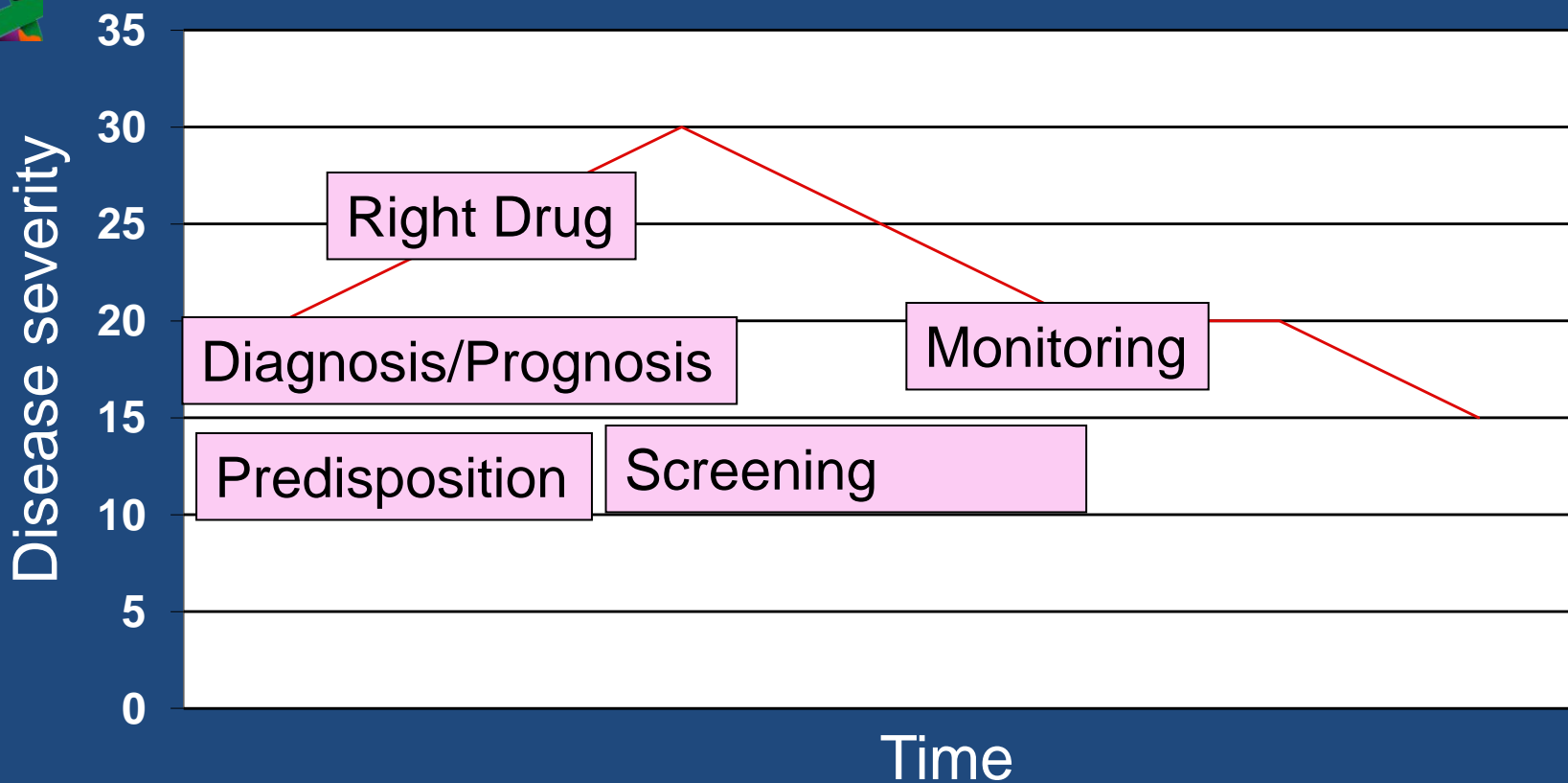
*Toward precision medicine*

# The old paradigm: Treatment of the disease



Reactive medical care

# More Effective Treatment Paradigm



Efficient medical care



> 1 in 4




**28%** of the novel new drugs approved by FDA in 2015 are personalized medicines

*Personalized Medicine Coalition, Jan. 2016*

# Nearly 160 Drugs with Genomic Information in the Label

Rx

Dx



**FDA** U.S. Food and Drug Administration  
Protecting and Promoting Your Health

A to Z Index | Follow FDA | FDA Voice Blog

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Home Food Drugs Medical Devices Vaccines, Blood & Biologics Animal & Veterinary Cosmetics Radiation-Emitting Products Tobacco Products

## Drugs

Home Drugs Science & Research (Drugs) Additional Research Areas

### Science & Research (Drugs)

- Additional Research Areas
- Genomics
- Overview of the Genomics Group
- Presentations on Genomics
- Publications on Genomics

### Table of Pharmacogenomic Biomarkers in Drug Labels

Pharmacogenomics can play an important role in identifying responders and non-responders to medications, avoiding adverse events, and optimizing drug doses. Drug labels may contain information on genomic biomarkers and can describe:

- Drug exposure and clinical response variability
- Risk for adverse events
- Genotype-specific dosing
- Mechanisms of drug action
- Polymorphic drug target and disposition genes

The table below lists FDA-approved drugs with pharmacogenomic information in their labels. Some, but not all, of the labels include specific actions to be taken based on genetic information. Relevant sections of the label with such information are noted in the last column of the table. Biomarkers may include gene variants, functional deficiencies, expression changes, chromosomal abnormalities, and others. Microbial variants that influence sensitivity to anti-infectives are not included in the table. Please note that the table columns can be sorted.

Pharmacogenomic information can appear in different sections of the label. For more information on the relevance of information in various parts of the drug label (e.g. Indications and Usage, Dosage and Administration, Boxed Warning, etc.), please go to the relevant [labeling guidance](#). For information on the FDA's initiative to improve prescription drug labels, visit the [FDA/CDER Learn website](#).

### Pharmacogenomic Biomarkers in Drug Labels

Drug	Therapeutic Area	Biomarkers	Label Sections
Abacavir	Antivirals	HLA-B*57:01	Boxed Warning, Contraindications, Warnings and Precautions, Patient Counseling Information
Arripiprazole	Psychiatry	CYP2D6	Clinical Pharmacology, Dosage and Administration



Rx

## PRECAUTIONS

**General:** PLAVIX prolongs the bleeding time and therefore should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or other pathological conditions (particularly gastrointestinal and intraocular). If a patient is to undergo elective surgery and an antiplatelet effect is not desired, PLAVIX should be discontinued 5 days prior to surgery.

Due to the risk of bleeding and undesirable hematological effects, blood cell count determination and/or other appropriate testing should be promptly considered, whenever such suspected clinical symptoms arise during the course of treatment (see **ADVERSE REACTIONS**).

In patients with recent TIA or stroke who are at high risk of recurrent ischemic events, the combination of aspirin and PLAVIX has not been shown to be more effective than PLAVIX alone, but the combination has been shown to increase major bleeding.

**Pharmacogenetics:** Based on literature data, patients with genetically reduced CYP2C19 function have lower systemic exposure to the active metabolite of clopidogrel and diminished antiplatelet responses, and generally exhibit higher cardiovascular event rates following myocardial infarction than do patients with normal CYP2C19 function (see **CLINICAL PHARMACOLOGY: Pharmacogenetics**).

**GI Bleeding:** In CAPRIE, PLAVIX was associated with a rate of gastrointestinal bleeding of 2.0%, vs. 2.7% on aspirin. In CURE, the incidence of major gastrointestinal bleeding was 1.3% vs. 0.7% (PLAVIX + aspirin vs. placebo + aspirin, respectively). PLAVIX should be used with caution in patients who have lesions with a propensity to bleed (such as ulcers). Drugs that might induce such lesions should be used with caution in patients taking PLAVIX.

atenolol and nifedipine. The pharmacodynamic activity of PLAVIX was also not significantly influenced by the coadministration of **phenobarbital**, **cimetidine** or **estrogen**.

The pharmacokinetics of **digoxin** or **theophylline** were not modified by the coadministration of PLAVIX (clopidogrel bisulfate).

At high concentrations *in vitro*, clopidogrel inhibits P<sub>450</sub> (2C9). Accordingly, PLAVIX may interfere with the metabolism of **phenytoin**, **tamoxifen**, **tolbutamide**, **warfarin**, **torsemide**, **fluvastatin**, and many **non-steroidal anti-inflammatory agents**, but there are no data with which to predict the magnitude of these interactions. Caution should be used when any of these drugs is coadministered with PLAVIX.

In addition to the above specific interaction studies, patients entered into clinical trials with PLAVIX received a variety of concomitant medications including **diuretics**, **beta-blocking agents**, **angiotensin converting enzyme inhibitors**, **calcium antagonists**, **cholesterol lowering agents**, **coronary vasodilators**, **antidiabetic agents** (including **insulin**), **thrombolytics**, **heparins** (unfractionated and LMWH), **GP1Ib/IIa antagonists**, **antiepileptic agents** and **hormone replacement therapy** without evidence of clinically significant adverse interactions.

There are no data on the concomitant use of oral anticoagulants, non study oral anti-platelet drugs and chronic NSAIDs with clopidogrel.

## Drug/Laboratory Test Interactions

None known.

## Carcinogenesis, Mutagenesis, Impairment of Fertility





# Multiplex Tests are Already Having an Impact

## OncoType DX (Breast Cancer)

Analyzes by qPCR, mRNA expression of a panel of 21 genes within a tumor to determine a Recurrence Score

## MammaPrint (Breast Cancer)

Microarray-based prognostic breast cancer mRNA expression profiling test of 70 genes

## AlloMap (Heart Transplants)

qPCR-based expression profile of 11 genes to assist physicians in managing heart transplant patients for potential organ rejection

## Tissue of Origin (15 common malignant tumor types)

Microarray technology considers 15 common malignant tumor types, including bladder, breast, and colorectal tumors based on mRNA expression on 1,550 genes

Rx

Dx



Source: Mara G. Aspinall, former President, Genzyme Genetics

# What will likely happen??

- Personalized medicine will involve pharmacogenomic treatment approaches that transcend the one-size-fits-all approach
- Personalized medicine will focus on keeping people well and treating disease at its earliest stages!
- Laboratory medicine will lead the way!
- Disease signatures comprised of hundreds or thousands of data points will be the biomarkers of the future
- Drug companies will develop their markets around interventional treatments for disease signatures!!



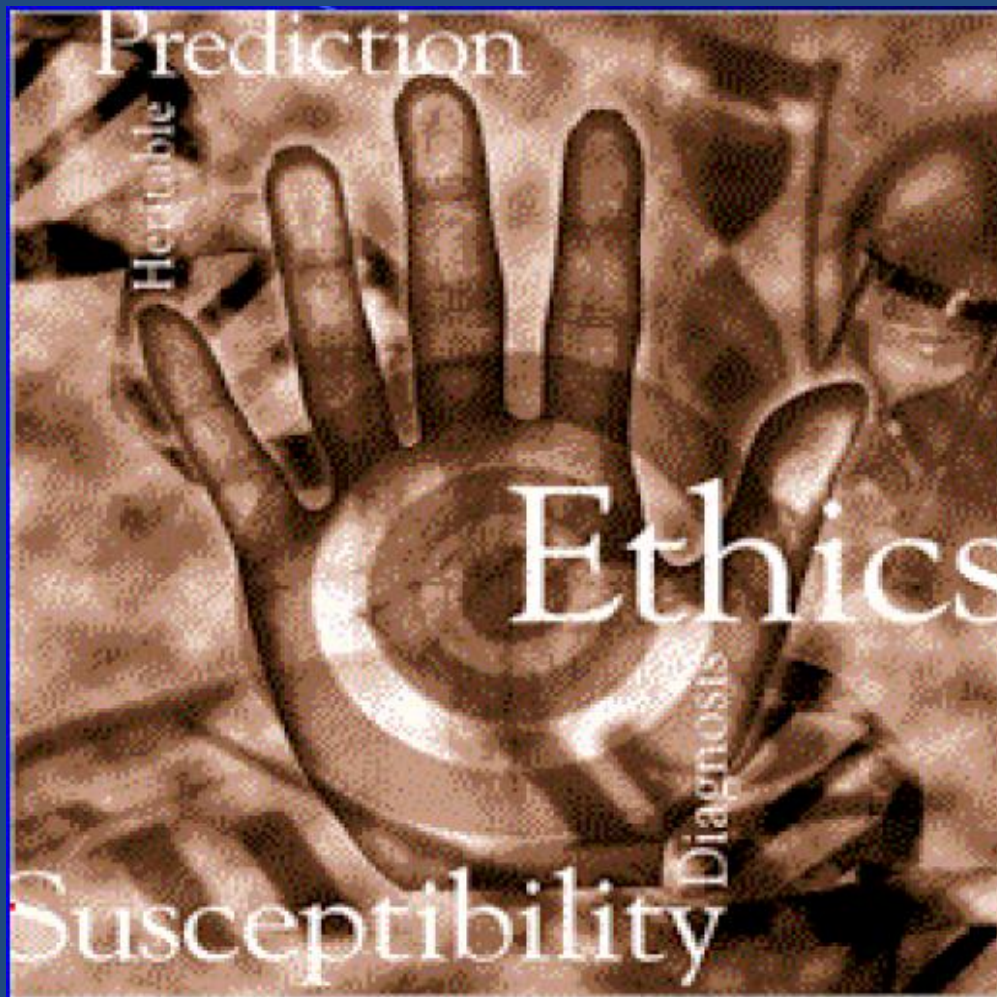
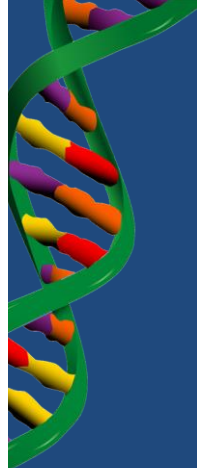
Rx



Dx







# AUTONOMY





# What Do Patients Want

Rx

Dx

## Provision of personalized genomic diagnostic technologies for breast and colorectal cancer: an analysis of patient needs, expectations and priorities

Several novel pharmacogenomic diagnostic tests are commercially available for breast and colorectal cancer and are increasingly being used in clinical practice for improving treatment decisions. However, there is a need for evidence evaluating the value of these new genomic technologies from the perspective of patients. The aim of an ongoing effort to understand the continuum of the process of adoption of genomic diagnostics, the focus of this study was to examine the value of genomic diagnostics to breast and colorectal cancer patients, and their willingness to adopt and use genomic diagnostics. **Patients & methods:** We conducted focus group discussions with groups of breast and colorectal cancer patients from the oncology clinics at The Methodist Hospital, Houston, TX, USA. An adapted Q-sort instrument was also administered to focus group participants. **Results:** The majority of breast and colorectal cancer patients are interested in using novel genomic diagnostics for making treatment decisions. Most participants in our study expressed a willingness to pay out-of-pocket for genomic testing ( $z = 0.736$ ). Reliability and validity of genomic testing were of significant concern ( $z = 0.736$ ) for the majority of breast and colorectal cancer patients. Participants identified several facilitators and barriers within health systems that might either facilitate or impede the widespread adoption and use of genomic diagnostics in healthcare delivery. **Conclusion:** This study demonstrates breast and colorectal cancer patients' willingness to adopt and pay for novel genomic diagnostics, as well as identifies several salient factors associated with patient preferences for genomic diagnostics.

**RDS:** breast cancer clinical adoption colorectal cancer focus groups genomic diagnostics patient expectations and priorities pharmacogenomics methodology

Amalia M Issa<sup>1,2,3</sup>,  
Janis F Hutchinson<sup>1,4</sup>,  
Waqas Tufail<sup>1</sup>,  
Erica Fletcher<sup>1</sup>,  
Roseline Ajike<sup>1,3</sup>  
& Jose Tenorio<sup>1,3</sup>

Previously reported on primary care readiness to accept and adopt the use of novel genomic diagnostics particularly for cancer care [15,16], it is critical to examine and measure patient preferences for the use of novel genomic diagnostics in breast

## Cancer patients' acceptance, understanding, and willingness-to-pay for pharmacogenomic testing

Sinead Cuffe<sup>a</sup>, Henrique Hon<sup>a</sup>, Xin Qiu<sup>b</sup>, Kimberly Tobros<sup>a</sup>, Chung-Kwun Amy Wong<sup>a</sup>, Bradley De Souza<sup>a</sup>, Graham McFarlane<sup>a</sup>, Sohaib Masroor<sup>a</sup>, Abul K. Azad<sup>a</sup>, Ekta Hasani<sup>a</sup>, Natalie Rozanec<sup>a</sup>, Natasha Leigh<sup>a</sup>, Shabbir Alibhai<sup>c</sup>, Wei Xu<sup>b</sup>, Amalia M. Issa<sup>d</sup> and Geoffrey Liu<sup>a</sup>

**Background** Pharmacogenomics is gaining increasing importance in the therapeutics of cancer; yet, there is little knowledge of cancer patients' attitudes toward the use of pharmacogenomic testing in clinical practice. We carried out this study to explore cancer patients' acceptance, understanding, and willingness-to-pay for pharmacogenomic testing.

**Materials and methods** A broad cross-section of gastrointestinal, lung, breast, and other cancer patients were interviewed in terms of their acceptance of pharmacogenomic testing using hypothetical time, efficacy, and toxicity trade-off and willingness-to-pay scenarios.

**Results** Among the 96% of 123 adjuvant patients accepting

making on pharmacogenomic testing; however, one in five patients lacked a basic understanding of pharmacogenomic testing.

**Conclusion** Among cancer patients willing to undergo chemotherapy, almost all wanted pharmacogenomic testing and were willing-to-pay for it, waiting several weeks for results. Although patients had a strong desire to be involved in decision-making on pharmacogenomic testing, a considerable proportion lacked the necessary knowledge to make informed choices. *Pharmacogenetics and Genomics* 24:348-355 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.

*Pharmacogenetics and Genomics* 2014, 24:348-355

## A national study of breast and colorectal cancer patients' decision-making for novel personalized medicine genomic diagnostics




**Aim:** Molecular diagnostics are increasingly being used to help guide decision-making for personalized medical treatment of breast and colorectal cancer patients. The main aim of this study was to better understand and determine breast and colorectal cancer patients' decision-making strategies and the trade-offs they make in deciding about characteristics of molecular genomic diagnostics for breast and colorectal cancer. **Patients & methods:** We surveyed a nationally representative sample of 300 breast and colorectal cancer patients using a previously developed web-administered instrument. Eligibility criteria included patients aged 18 years and older with either breast or colorectal cancer. We explored several attributes and attribute levels of molecular genomic diagnostics in 20 scenarios. **Results:** Our analysis revealed that both breast and colorectal cancer patients weighted the capability of molecular genomic diagnostics to determine the probability of treatment efficacy as being of greater importance than information provided to detect adverse events. The probability of either false-positive or -negative results

# The Patient Preferences for Personalized Medicine Instrument™ : Simulating Real-World Decision-Making

We would like you to consider an imaginary scenario not related to you. Please imagine you have just recovered from surgery to remove a tumor. Your doctor has offered a [genomic test](#) to help you decide on treatment options. You will not have to undergo any additional invasive procedures for the test.

The results from the test will predict whether or not you are likely to benefit from chemotherapy. With these tests, patients who are unlikely to benefit from chemotherapy can avoid receiving such treatment and therefore avoid any side effects.

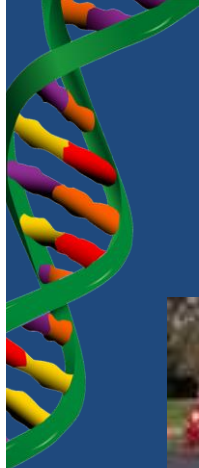
Please imagine you were in the situation described above and assume the options below were the only tests available. Please choose the test that you **most** prefer, and then please indicate whether you really would be willing to take the test you selected if you were in this situation.

What is the cost of testing to you personally?	\$2,000	\$500	\$4,000
How will your test results be used?	You will decide how to use the test results, regardless of your risk of recurrence	Your doctor will decide how best to treat you based upon your results (for example if testing suggests that your risk of recurrence is low, you may not receive chemotherapy)	Your insurance company will use the test results to determine your coverage (for example if testing suggests that your risk of recurrence is low, your insurance company may not cover the cost of chemotherapy)
The chance the test will <u>correctly predict</u> patients' response to treatment	96% (96 out of 100 tests will correctly predict response to treatment) 	70% (70 out of 100 tests will correctly predict response to treatment) 	80% (80 out of 100 tests will correctly predict response to treatment) 
What information will the test provide?	Predict how likely you are to benefit from chemotherapy and how likely you are to develop severe side effects from chemotherapy.	<u>Recurrence risk</u> that cancer will return (stated as either low, medium or high risk); predict how likely you are to benefit from chemotherapy and how likely you are to develop severe side effects from chemotherapy.	Predict how likely you are to benefit from chemotherapy.
Who has access to your test results?	Patient and doctor	Patient, doctor and insurance company	Patient, doctor, insurance company and employer
	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Given what you know about the test, please indicate whether you really would be willing to take the test you selected above if you were in this situation?

- ☐ Yes
- ☐ No

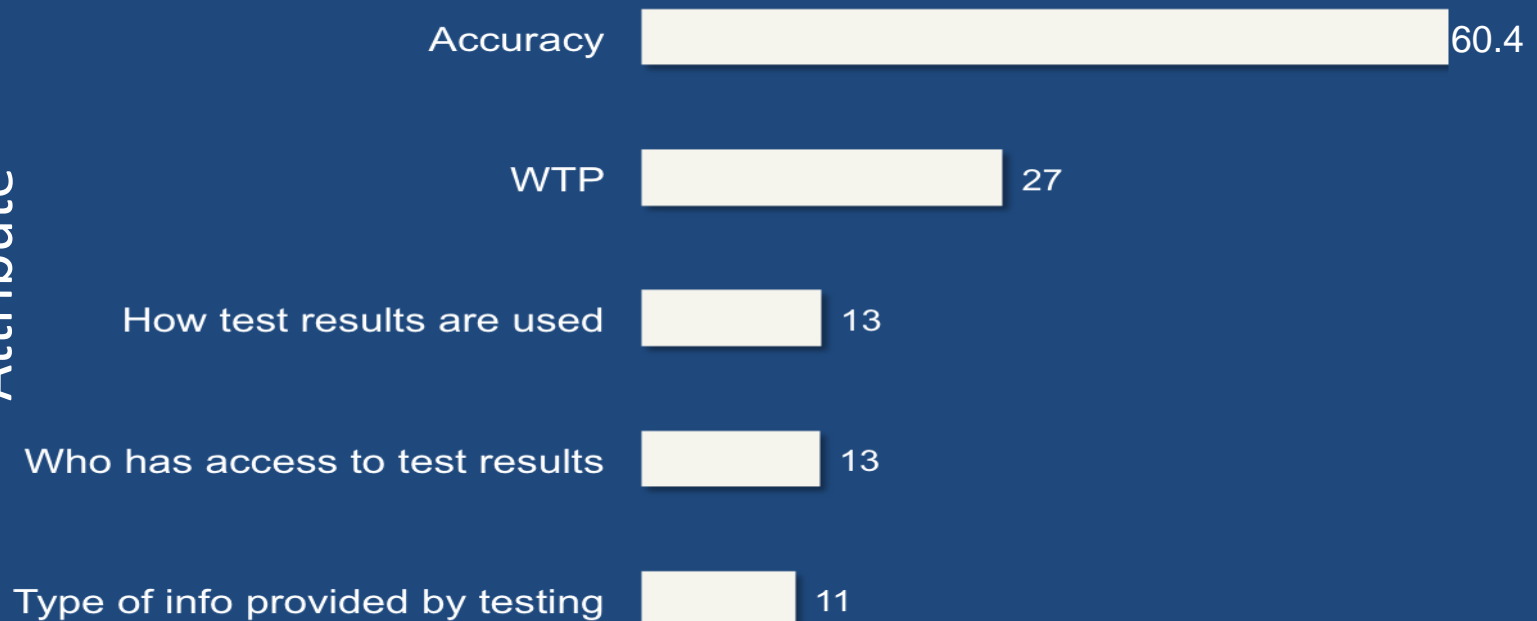




Attributes	Levels
Color	Black White Red
Size	SUV Truck Sedan
Doors	2-door 4-door

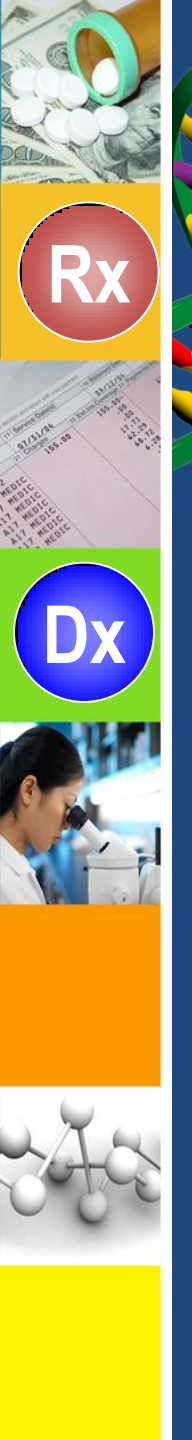
# All attributes impact patients' decisions but Accuracy and WTP carry most weight

Attribute

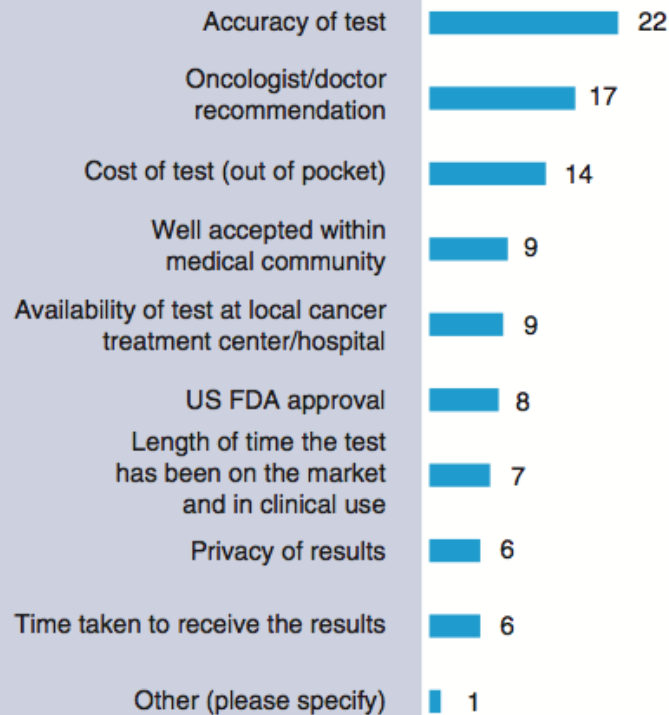


Relative Importance (%)

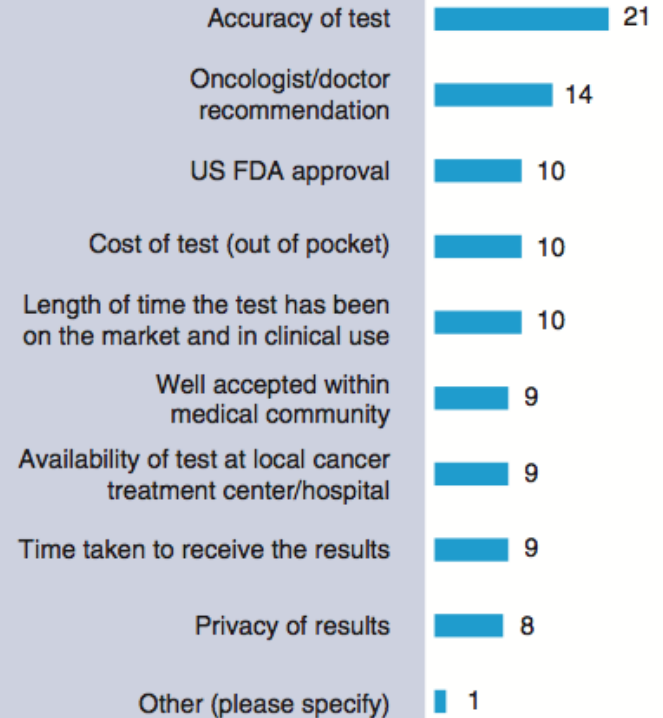
# Attribute Relative Importance by Cancer Type



## Breast cancer



## Colorectal cancer



# What We've Learned...

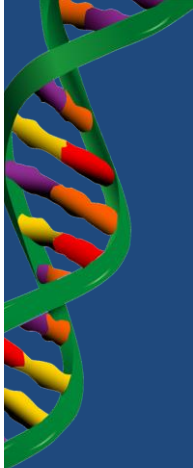
- Among various populations, patients are overwhelmingly willing to accept, pay for and use genomic diagnostic tests and personalized med. applications.
- Willingness to pay falls predictably at increasingly higher costs, however patients are willing to pay a higher cost if it would prevent insurance companies from having access to test results.
- Patients want physicians to be intermediaries (contrary to conventional wisdom and lit about pt. autonomy) when deciding about genomic testing. They want physicians to make specific recommendations.
- Test accuracy, specificity, sensitivity, and no false positive or false negative results were among most important attributes for patients.
- Patients want results of testing fast.







- Attribute 'privacy' initially not ranked high
- 'Doctor recommendation' ranked highly
- Pts expect high accuracy; acceptance by medical community and FDA of tests is important
- Patients trade-off privacy concerns for benefit
- Suggests that docs are indispensable intermediaries; somewhat contradicts lit. on pt. autonomy
- Challenges assumption that pts don't care about technical aspects



After a short stay in America, Michelangelo's  
David Returned to Europe

# Identifying Personal Genomes by Surname Inference

Melissa Gymrek,<sup>1,2,3,4</sup> Amy L. McGuire,<sup>5</sup> David Golan,<sup>6</sup> Eran Halperin,<sup>7,8,9</sup> Yaniv Erlich<sup>1\*</sup>

Sharing sequencing data sets without identifiers has become a common practice in genomics. Here, we report that surnames can be recovered from personal genomes by profiling short tandem repeats on the Y chromosome (Y-STRs) and querying recreational genetic genealogy databases. We show that a combination of a surname with other types of metadata, such as age and state, can be used to triangulate the identity of the target. A key feature of this technique is that it entirely relies on free, publicly accessible Internet resources. We quantitatively analyze the probability of identification for U.S. males. We further demonstrate the feasibility of this technique by tracing back with high probability the identities of multiple participants in public sequencing projects.

Surnames are paternally inherited in most human societies, resulting in their cosegregation with Y-chromosome haplotypes (1–5). Based on this observation, multiple genetic genealogy companies offer services to reunite distant patrilineal relatives by genotyping a few dozen

highly polymorphic short tandem repeats across the Y chromosome (Y-STRs). The association between surnames and haplotypes can be confounded by nonpaternity events, mutations, and adoption of the same surname by multiple founders (5). The genetic genealogy community addresses these barriers with massive databases that list the test results of Y-STR haplotypes along with their corresponding surnames. Currently, there are at least eight databases and numerous surname project Web sites that collectively contain hundreds of thousands of surname-haplotype records (table S1).

The ability of genetic genealogy databases to breach anonymity has been demonstrated in the past. In a number of public cases, male adoptees and descendants of anonymous sperm donors used recreational genetic genealogy services to genotype their Y-chromosome haplotypes and to search the companies' databases (6–9). The genetic matches identified distant patrilineal relatives and pointed to the potential surnames of their biological fathers.

By combining other pieces of demographic information, such as date and place of birth, they fully exposed the identity of their biological fathers. Lunshof *et al.* (10) were the first to speculate that this technique could expose the full identity of participants in sequencing projects. Gitschier (11) empirically approached this hypothesis by testing 30 Y-STR haplotypes of CEU participants in these

**“Surnames can be recovered from personal genomes by profiling short tandem repeats on the Y chromosome (Y-STRs) and querying recreational genetic genealogy databases.”**

terms did not prevent re-identification. Representatives of relevant organizations that funded the original studies were notified and confirmed the compliance of this study with their guidelines (12).

As a primary resource for surname inference, we focused on Ysearch ([www.ysearch.org](http://www.ysearch.org)) and

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\*To whom correspondence should be addressed. E-mail: [yaniv@wi.mit.edu](mailto:yaniv@wi.mit.edu)

# What MIT Group Did

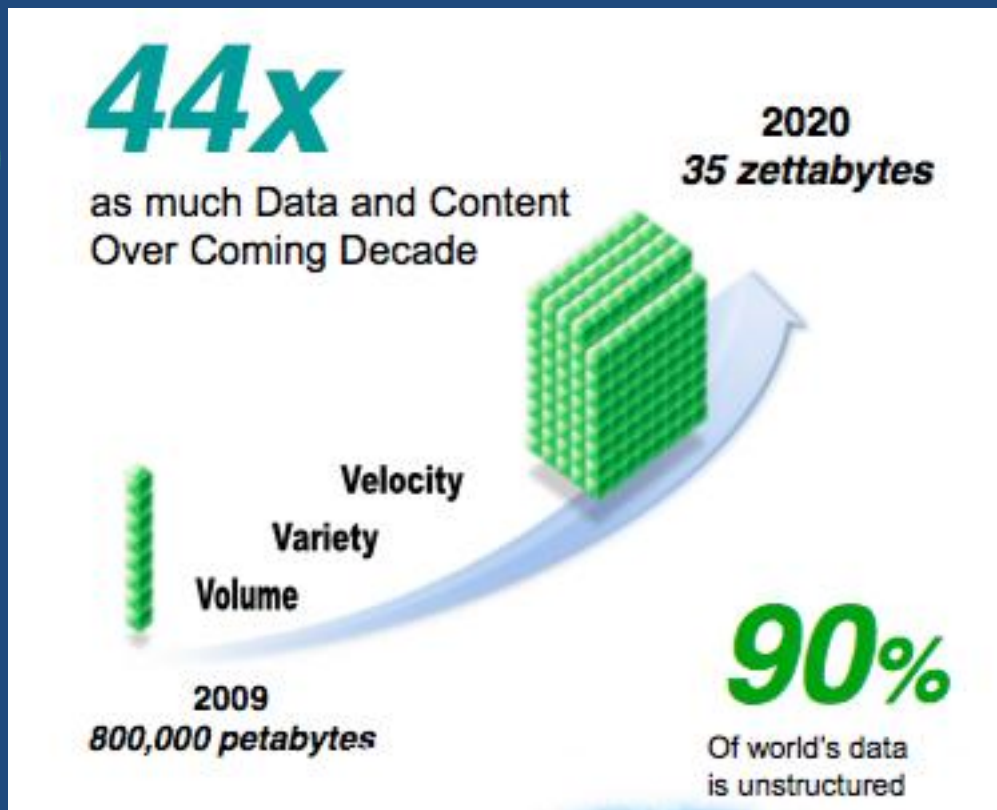


Rx

Dx

- 1000 Genomes Project database
- Includes participants' age and region where they live (all Americans are from CEPH population in Utah)
- Pulled out short tandem repeats on Y chromosome and matched to genetic genealogy database to get surname
- Did a Google search to find obituary and was able to identify entire family tree
- Identified nearly 50 people this way – published method, not names of people identified





# The Revenant



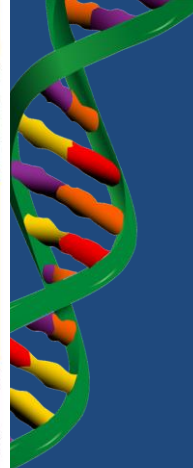
# The Revenant

Rx

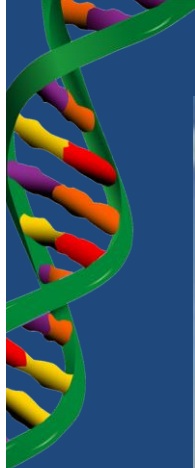
Dx



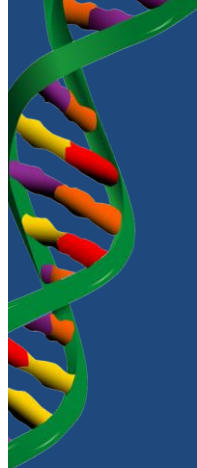


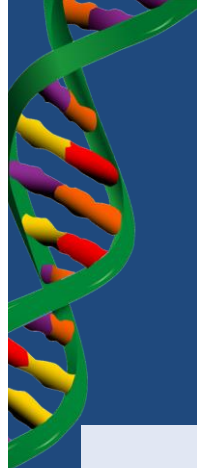






**Eyjafjallajökull volcanic eruption  
Iceland, 2010**







# Critical Question:

**What concentration of volcanic ash is harmful to jet engines?**



# Archbishop S. Tomasi:



- “The fruits of scientific progress, rather than being placed at the service of the entire human community, are distributed in such a way that inequalities are actually increased.”
- He then quoted St. John Paul II’s statement to the Jubilee 2000 Debt Campaign:
- “The law of profit alone cannot be applied to that which is essential for the fight against hunger, disease, and poverty.”

# How can the Church contribute to the dialogue?

Rx



*Here There be Dragons!*



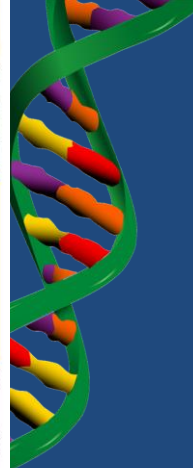
# Multi-level Factors Affecting Implementation of PM



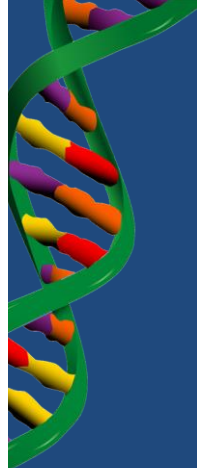
Rx

Dx

- Point of care (MD knowledge, patient demand)
- Microsystem, team (norms, culture)
- Clinic, hospital (policies, leadership)
- Delivery system (organizational/fiscal policies, leadership, resources)
- Professional norms (local, regional, national)
- Patients, businesses, other stakeholders (community, region, province/state, nation)
- Local, regional, national regulations







# Laron Syndrome



Growth Hormone Receptor Deficiency Is Associated with a Major Reduction in Pro-Aging Signaling, Cancer, and Diabetes in Humans

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# The Alternative



He has sent me to proclaim liberty to captives  
and recovery of sight to the blind;

and to proclaim a year acceptable to the Lord.”

**(Luke 4:18-19)**