The Personalized Medicine Revolution
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Author: “The Personalized Medicine Revolution: How Diagnosing and Treating Disease Are About to Change Forever”
Professor: University of British Columbia, Canada
Problems With Current Healthcare

- Current healthcare is “sick-care”, people treated after getting ill, disease often detected too late, leads to high costs and limited treatment success;
- Many drugs harm or don’t work on the patients they are prescribed for;
- Healthcare consumers do not have adequate information to practice effective preventive healthcare, particularly diet and exercise;
- Most healthcare employs a “one size fits all” approach which ignores the fact we are all different!
Current Medicine: “One Size Fits All” Healthcare

The problem is, we are all very different!
These Differences Are Major Determinants of Our Health

- Genetics: 30%
- Health Care: 10%
- Age, behavior & environment: 60%
We Are All Very Different From One Another

1) Different genetic makeup from birth
   - Up to three million differences in genetic makeup between you and anybody else (sex, ethnicity, physical appearance etc.)

2) We get even more different as we get older
   - Differences due to our age, lifestyle, nutrition, exercise
   - Differences due to our environment: climate, pollution, bacteria living in and on our bodies
   - Different diseases (e.g. every cancer is a rare disease), drug regimes etc.

All these differences are reflected by differences in the molecular makeup of our bodies
Molecular data-clouds for each individual

Well people, ill people

Detection of trends towards disease
Effective preventive medicine
Early detection of disease
Precise diagnosis
Individualized therapies
Monitor response to therapy
1. Power will move from the healthcare system to you, the healthcare consumer. Individualized molecular analyses will:
   - Provide accurate diagnoses of what is wrong with you
   - Prescribe personalized therapies that are best for you
   - Provide ways to monitor whether therapy is effective
   - Prescribe ways to practice effective preventive healthcare

2. Medical care will shift from treating people after they become ill to preventing them getting ill (sick-care to healthcare)
   - Your doctor will increasingly become your health coach
Personalized medicine relies on new technologies that characterize individuals at the molecular level.
The cost of sequencing a human genome has decreased by nearly a million-fold since 2000.
Personalized Medicine Is Enabled By Huge Advances in Molecular Profiling (“Omic”) Technology

1. **Genomic**: Sequence a human genome (~$1,000)

2. **Proteomic**: Analyze 100 proteins in blood

3. **Metabolomic**: Analyze 100 metabolites in blood, urine

4. **Microbiomic**: Analyze 1,000 bacteria in your intestines

5. **Analytical**: Advances in information technology allow all this data to be stored and analyzed very inexpensively

Molecular profiling is becoming more comprehensive and increasingly inexpensive
Forces Driving Adoption of Personalized Medicine Based on Molecular Profiling

1. Rapid technological change (inexpensive molecular level analyses, information technology)

2. Patient safety (adverse drug reactions are the 4th leading cause of death)

3. Drug efficacy ( >50% of drugs don’t work for individuals they are prescribed for)

4. Preventive medicine (need individualized, definitive data to avoid trending toward disease)

5. Consumer demand: want better ways to treat disease and maintain health!
Patient Safety: Adverse Drug Reactions Are the Fourth Leading Cause of Death in North America

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Number of deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart disease</td>
<td>743,460</td>
</tr>
<tr>
<td>Cancer</td>
<td>529,904</td>
</tr>
<tr>
<td>Stroke</td>
<td>150,108</td>
</tr>
<tr>
<td>Adverse drug reactions</td>
<td>106,000 (range 76,000-137,000)</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>101,077</td>
</tr>
<tr>
<td>Accidents</td>
<td>90,523</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>75,523</td>
</tr>
<tr>
<td>Diabetes</td>
<td>53,894</td>
</tr>
</tbody>
</table>

90% of adverse drug reactions are not reported
Adverse Drug Reaction: Doxorubicin-Induced Heart Toxicity

- Anticancer drug doxorubicin (used for 70% of childhood cancers, breast cancer patients, 1M patients/yr)
- 10-30% of patients suffer heart failure; increased severity in children
- May cause death, require heart transplant or reduced heart function that lasts a lifetime
- Some people are much more susceptible than others due to their genetic makeup
Adverse Drug Reaction Example: Doxorubicin-Induced Heart Toxicity

- 12 year-old boy presents with pain in abdomen
- Diagnosed with lymphoma
- Undergoes chemotherapy
- After second round of chemotherapy becomes breathless after walking a few steps
- Diagnosed with heart failure
- Requires heart transplant

Could have been prevented by a simple genetic test
What About Adverse Reactions to Drugs Used to Treat Other Diseases?

The more drugs you take the greater the chance of an adverse drug reaction
We Take a Lot of Prescription Drugs

20% of people over 65 take 10 or more drugs every day
Personalized Medicine: Genetic Tests For Drug Prescription

Problem:

- Over 100,000 deaths per year in North America are due to adverse reactions to prescription drugs
- Usually due to differences in genetic makeup

Solution:

- For ~150 common drugs there is genetic guidance on the package insert
- Not used currently because the doctor does not know the genetic profiles of his patients
- Can use a simple genetic test to guide drug prescription
Current Genetic Guidance in Package Insert for Allopurinol, a Gout Medication!

<table>
<thead>
<tr>
<th>Class / Pregnancy category</th>
<th>Side effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Indomethacin at once, headache, TSE, GI problems, HF, transplant Precautions</td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>Rare, Serious Precautions: Liver &amp; biliary to patients who have or develop peptic ulcer disease, glomerulonephritis, or are young men; elderly women who are more sensitive to GI effects</td>
<td></td>
</tr>
<tr>
<td>Corticosteroids/</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metoclopramide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allopurinol ZYLOPRIN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Febuxostat</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycolic acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAIDs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Betablockers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antacids</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**What is the content of diyuresis with gout?**
- Increased uric acid concentration in serum
- Hydrochloric acid induced gout
- Risk factor for gout
- Red flag for gout

**What are the primary drug treatment options for gout?**
- Acute attack: Use aminosalicylic acid
- Chronic treatment: Prevent future attacks

**Maintenance: useful & may + the need for preventive medications**
- Diet: control with low purine diet is poor
- Medications: use of antifib~colic drugs is preferred
- Preventive remedies: use of allopurinol

**Lifestyle & Weight loss:**
- Smoking cessation: 1 alcohol unit (equally be used) 
- 24-36 daily activity (unless CI) need mild-intensity exercise

**Are there any special treatment considerations?**
- Gout attack: Use of short-term anti-inflammatory drugs
- Chronic treatment: Use of allopurinol

**What are the primary drug treatment options for gout?**
- Acute attack: Aminosalicylic acid
- Chronic treatment: Prevent future attacks

**Maintenance: useful & may + the need for preventive medications**
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**Are there any special treatment considerations?**
- Gout attack: Use of short-term anti-inflammatory drugs
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[Other relevant information and figures provided in the package insert are omitted for brevity.]
Personalized Medicine: Genetic Tests To Avoid Adverse Reactions to Prescription Drugs

GenXys Healthcare Systems

Genetic test (in EMR) → Physician diagnosis → Computer algorithm → Personalized prescription → Fewer adverse drug reactions, More efficient healthcare
Drug Efficacy: Less Than 50% of Drugs Work on the Patient They are Prescribed For

<table>
<thead>
<tr>
<th>Drug</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Depressants</td>
<td>62 %</td>
</tr>
<tr>
<td>Asthma</td>
<td>60 %</td>
</tr>
<tr>
<td>Diabetes</td>
<td>57 %</td>
</tr>
<tr>
<td>Arthritis</td>
<td>50 %</td>
</tr>
<tr>
<td>Alzheimer</td>
<td>30 %</td>
</tr>
<tr>
<td>Cancer</td>
<td>25 %</td>
</tr>
</tbody>
</table>
How Can Personalized Medicine Help Prevent Adverse Drug Reactions and Ensure Efficacy?

Need to use molecular profiles to “stratify” patients so they receive the most appropriate therapy.
Example: Genetic Tests To Guide Drug Prescription For Cancer Treatment

Problem:
- 75% of cancer drugs do not work on the person they are given to
- All cancer drugs can be very toxic

Solution:
- Sequence the cancer genome to determine cancer-causing mutations
- Sequence the normal genome to determine potential for adverse drug reactions
- Treat cancer with drugs that target the mutations and minimize toxicity
Personalized Medicine: Genetic Tests To Guide Drug Prescription For Cancer Treatment

- Same diagnosis
- Test to see which drugs will be safe and effective
- Match therapy to the patient

Molecular Profiling → Prognostic Markers → Match therapy to the patient
Genetic Analyses of the Cancer Genome Can Revolutionize Cancer Treatment

- Trish Keating: diagnosed with colon cancer 6 years ago
- Multiple rounds of chemotherapy, relapsed each time
- Stage 4 cancer-disseminated throughout her body
- Cancer genome sequenced, cancer cells relied on a gene that could be inhibited by a blood pressure drug
- Six weeks after treatment cancer disappeared, still in remission 2 yr later
However, Analyses of Your Native Genomic DNA Are Not That Useful For Predicting or Diagnosing Most Diseases

Need to measure other molecules in your body

First, need to explain how the reliability of “biomarkers” that indicate the presence of disease is characterized
Assessing The Reliability of Biomarkers For Disease Using Receiver-Operator Curves (ROC)

- Plots sensitivity vs. specificity
- A poor ROC curve would be a straight line with a slope of 1
- The area under an ROC curve (AUC) is a good measure of the quality of the biomarker
- AUCs of >0.75 are good, AUCs of 0.5 are terrible, AUCs of 1.00 are perfect
Analyses of Your Genomic DNA Are Not That Useful For Predicting Risk for Most Diseases: Breast Cancer

**Study:** HGVST1616

**Dataset:** HGVRS3305

Sample size:
- 12575 controls
- 10052 cases

Genetic analysis
- 62 SNPs

**AUC=0.56**

Area under the curve (AUC) = 0.562

95% CI: 0.554 – 0.569
Analyses of Your Genomic DNA Are Not That Useful For Predicting Risk For Most Diseases: Colorectal Cancer

Study:
HGVST1469

Dataset:
HGVRS2702

Sample size:
15113 controls
2696 cases

Genetic analysis
15 SNPs

AUC=0.53

Area under the curve (AUC) = 0.527
95% CI: 0.52 – 0.533
Need Additional Molecular Profiles To Detect the Presence of Most Diseases: The “Omics”

You: Your genes code for proteins which produce metabolites

Your microbiome: bacteria, fungi and viruses that live in you and on you

Genomics  Proteomics  Metabolomics  Microbiomics

The “Omics”
Your Blood Contains Many Proteins and Metabolites That Can Be Used to Detect and Diagnose Disease

Each organ secretes proteins and metabolites into the blood that can be diagnostic for the health of that organ:

- Early detection of disease
- Monitor disease progression
- Monitor effects of therapy
- Detect re-occurrence of disease

We can now detect hundreds of proteins and metabolites in your blood simultaneously to diagnose disease anywhere in your body.
Most Proteomic & Metabolomic Data is Highly Diagnostic: Kidney Transplant Rejection

Current biopsy procedure very costly and invasive

Urine sample
9 metabolites

AUC = 0.96
Proteomic and Metabolomic Profiling Improves on Standard Diagnostic Tests

Colonic polyps
Urine Samples
AUC = 0.78 (12 metabolites)

Esophageal cancer
Urine Samples
AUC = 0.98 (7 metabolites)

Fecal occult blood test – AUC=0.63

Carcinogenic embryonic antigen test: AUC=0.74
Proteomic and Metabolomic Data Profiling Improves on Standard Diagnostic Tests

Prostate Specific Antigen (PSA) Test

Prostate Cancer blood test (3 metabolites)

AUC = 0.65

AUC = 0.93

Area under the curve (AUC) = 0.932
95% CI: 0.867 - 0.979
Your Microbiome: The Bacteria Living In and On Your Body Can Also Influence Your Health

You contain 10 times as many bacterial cells as human cells; your “microbiome”. The wrong microbiome can contribute to:

- Inflammatory bowel disease
- Diabetes
- Rheumatoid arthritis
- Muscular dystrophy
- Multiple sclerosis
- Obesity
- Autism (?)

We can measure a thousand or more bacteria in your gut (fecal sample) to characterize your microbiome.
Molecular data-clouds for each individual

- Well people, ill people
- Phenotype
- Proteomic
- Genomic
- Metabolomic
- Microbiomic
- Other “Omics”

Detection of trends towards disease
Effective preventive medicine
Early detection of disease
Precise diagnosis
Individualized therapies
Monitor response to therapy

The Future of Medicine: Improved Healthcare Through Comprehensive “Omic” Profiling
Molecular You Omic Profiling

YOU

Genes
Genomics

Proteins
Proteomics

Metabolites
Metabolomics

Bacteria
Microbiomics

MOLECULAR YOU
Molecular You Omic Profiling

Genetic Profile
- Analysis of genome sequence:
  - 700,000 SNPs

Protein Profile
- Analysis of proteins in the blood:
  - ~150 proteins

Microbial Profile
- Analysis of bacteria in gut:
  - >1,000 bacteria

Metabolite Profile
- Analysis of small molecules in blood:
  - ~150 metabolites

> 100 clinically approved biomarkers

~100 clinically approved biomarkers
The Molecular You Process

- Doctor
- Patient
- Action plan
- Comparative analysis
- “multi-Omic” data cloud
- Samples
Your Data Cloud is Compared to a Curated Reference Database

World’s clinical information: Omic biomarkers associated with more than 300 diseases (1-12 clinical studies per disease)

“Big data” storage and analytics

Disease-associated outliers
The Molecular You Analysis Provides Diagnostics/Risks for >300 Diseases

- Heart disease
- Diabetes
- Hypertension
- Stroke
- Breast cancer
- Prostate cancer
- Colon cancer
- Lung cancer
- IBD
- Pancreatic cancer
- Dementia
- Depression
- Autism
- Osteoporosis
- Arthritis
- Kidney disease
- Pneumonia
- COPD
- Multiple myeloma
- Leukemia
- etc
Omic Profiling Can be Used for Preventive Medicine and Disease Treatment

- **Well people**
  - Snapshot of health
  - Detect trends towards disease
  - Suggest diet/exercise-supplements etc to avoid disease
  - Ascertain whether therapy is working

- **Ill people**
  - Diagnose disease
  - Match therapy to disease
  - Ascertain whether therapy is working
Snapshot of your health:

- Level 1: Overview
  - a top line summary of your health and top disease risks
- Level 2: Disease risk report (>300 diseases)
- Level 3: Organ/system health summary
  - Brain, GI tract, heart, immune system, joint/muscle, kidney, liver, etc
- Level 4: Details of organ/system health
  - Scientific literature
The MYCO Report Ranks Your Risk of Disease Based on Your Omic Profile

**Tested:** Multiple factors associated with this health condition have been evaluated but either none of these are outside of the normal range OR not enough of these factors are outside the normal range to signal anything of concern.

**Green:** A number of factors may be outside of the normal range; however, any associated indicated health conditions should not be concerning.

0.0 - 3.4

**Yellow:** Some factors associated with this health condition are outside of the normal range. Your health status may be trending towards this condition. Please take the appropriate physician recommended actions.

3.5 - 5.9

**Red:** Many factors associated with this health condition are outside of the normal range. Your health status is trending rapidly towards this condition. Please take the appropriate physician recommended actions as soon as possible.

6.0 -
Your current results don't indicate any known risk for your health.

We measured 24.5 thousand SNPs, 173 metabolites, 154 proteins and 16 categories of microbes.

**Highest Disease Risks**

- 3.4 Diabetes
- 2.6 Heart disease
- 2.4 Lung cancer
The MYCO Report for Pieter Cullis: Other Diseases Tested For

<table>
<thead>
<tr>
<th>Condition Name</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver Cirrhosis</td>
<td>TESTED</td>
</tr>
<tr>
<td>Lupus erythematosus</td>
<td>TESTED</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>TESTED</td>
</tr>
<tr>
<td>Arterial thrombosis</td>
<td>TESTED</td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>TESTED</td>
</tr>
<tr>
<td>Local clotting</td>
<td>TESTED</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>TESTED</td>
</tr>
<tr>
<td>Cartilage damage</td>
<td>TESTED</td>
</tr>
<tr>
<td>Joint injury</td>
<td>TESTED</td>
</tr>
<tr>
<td>Arthritis</td>
<td>TESTED</td>
</tr>
<tr>
<td>Tissue damage</td>
<td>TESTED</td>
</tr>
<tr>
<td>Heart disease</td>
<td>TESTED</td>
</tr>
<tr>
<td>Heart attack</td>
<td>TESTED</td>
</tr>
<tr>
<td>Crohn's disease</td>
<td>TESTED</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>TESTED</td>
</tr>
<tr>
<td>Liver failure</td>
<td>TESTED</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>TESTED</td>
</tr>
<tr>
<td>Tyrosinemia</td>
<td>TESTED</td>
</tr>
<tr>
<td>Melanoma</td>
<td>TESTED</td>
</tr>
<tr>
<td>Stroke</td>
<td>TESTED</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>TESTED</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>TESTED</td>
</tr>
</tbody>
</table>

Etc. for another ~300 diseases
What Are The Diabetes Markers?

Diabetes mellitus (DM), commonly referred to as diabetes, is a group of metabolic diseases in which there are high blood sugar levels over a prolonged period.

We measured a total of 60 molecular measures related to diabetes. 2 measures are outside of the usual normal ranges and may reflect issues related to this system.

Molecular Measures

<table>
<thead>
<tr>
<th>Measure</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteomic</td>
<td>0</td>
</tr>
<tr>
<td>Metabolomic</td>
<td>1</td>
</tr>
<tr>
<td>Genomic</td>
<td>2.4</td>
</tr>
<tr>
<td>Microbiomic</td>
<td>0</td>
</tr>
</tbody>
</table>
What Are The Diabetes Markers?

<table>
<thead>
<tr>
<th>MEASURE NAME</th>
<th>VALUE</th>
<th>VALUE WITHIN RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tyrosine</td>
<td>🔺 83.4 μM</td>
<td><img src="chart1.png" alt="Tyrosine chart" /></td>
</tr>
<tr>
<td>rs3184504 (T;T)</td>
<td>3</td>
<td><img src="chart2.png" alt="rs3184504 chart" /></td>
</tr>
</tbody>
</table>
What About Someone Who Has Problems?

This is “Mike”

What can “Mike” do lower his risk score?

<table>
<thead>
<tr>
<th>Condition</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>6.3</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>6.2</td>
</tr>
<tr>
<td>Hemoglobinemia</td>
<td>6.0</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>5.8</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>5.8</td>
</tr>
<tr>
<td>Pre-diabetes</td>
<td>5.6</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>4.1</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>3.0</td>
</tr>
<tr>
<td>Infection</td>
<td>2.8</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>2.8</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>2.8</td>
</tr>
</tbody>
</table>
MYCo Compares Disease-Associated Outliers to World’s Therapeutic Information to Develop an Action Plan

World’s therapeutic information: What actions can arrest or reverse Omic biomarkers trending towards disease?

Personalized action plan
## Components of Action Plan

<table>
<thead>
<tr>
<th>Diet (Nutritionist)</th>
<th>Exercise (Kinesiologist)</th>
<th>Supplements (Naturopath or MD consultation)</th>
<th>Pharmacogenomics (Geneticist)</th>
<th>Medical/Pharmaceutical (MD consultation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foods to avoid/include in diet</td>
<td>Exercise program tailored to you</td>
<td>Supplements to counteract molecular deficiencies (e.g. neurotransmitters)</td>
<td>Drugs to avoid/adjust dose</td>
<td>Disease diagnosis/treatment</td>
</tr>
</tbody>
</table>
Early Detection of Trends Towards Disease Will Allow Effective Preventive Care

Preventive care: personalized diet, exercise, supplement programs based on your data
Quantitative Health: Molecular Profiling Will Provide Data You Need to Achieve Better Health

Where are you on the health staircase?

All of us will have actionable findings
All of Us Will Have Actionable Findings Such As Vitamin D Supplements

Vitamin D deficiency arises from genetics and environment

- ~90% of North Americans are low in Vitamin D
- Six genetic variants from 3 genes block Vitamin D absorption
- Those with multiple blocking variants need mega-doses of Vitamin D

Risks associated with low Vitamin D

- Ricketts—improper bone mineralization
- Increased risk of death from cardiovascular disease
- Cognitive impairment in older adults—Alzheimer’s
- Severe asthma in children
- Cancer
All of Us Will Have Actionable Findings That Require An Exercise Prescription!

- We are designed to be active, our genes were developed to sustain high physical activity
- Inactivity activates disease causing genes
- Exercise prevents 26 chronic conditions as effectively as any drugs available
- A standardized exercise test is a better predictor of mortality than hypertension, obesity, and insulin resistance combined
Personalized Medicine Will Revolutionize Healthcare

Molecular Profiling

Detection of trends towards disease
Detection of early stage disease
Accurate diagnosis of disease
Targeted therapy
Monitor effectiveness of therapy

Benefits

Patient empowerment
Effective preventive medicine
Effective, non-toxic therapy
No more trial and error!
“The Personalized Medicine Revolution: How Diagnosing and Treating Disease Are About to Change Forever”

If you want to learn more, you can read the book! 