Precision medicine: The future of personalized healthcare

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Preview of take home points

• Genomic knowledge exploding
  – Very little known right now

• Knowledge is key to understanding the genome
  – Few approaches to leverage knowledge

• Dynamic transcriptome can be challenged *in vitro* to unveil ineffective or adverse medication before prescription
Plan

• Precision medicine initiative of the White House
  – bipartisan
• Complexity of the personal genome
• Mechanism-anchored transcriptome interpretation
• Dynamics of personal transcriptome & interpretation
WHAT IS IT?

Precision medicine is an emerging approach for disease prevention and treatment that takes into account people's individual variations in genes, environment, and lifestyle. The Precision Medicine Initiative will generate the scientific evidence needed to move the concept of precision medicine into clinical practice.

WHY NOW?

The time is right because of:

- Sequencing of the human genome
- Improved technologies for biomedical analysis
- New tools for using large datasets

NEAR-TERM GOALS

- Intensify efforts to apply precision medicine to cancer.
- Innovative clinical trials of targeted drugs for adult, pediatric cancers
- Use of combination therapies
- Knowledge to overcome drug resistance

LONGER-TERM GOALS

- Create a research cohort of > 1 million American volunteers who will share genetic data, biological samples, and diet/lifestyle information, all linked to their electronic health records if they choose.
- Pioneer a new model for doing science that emphasizes engaged participants, responsible data sharing, and privacy protection.
- Research based upon the cohort data will:
  - Advance pharmacogenomics, the right drug for the right patient at the right dose
  - Identify new targets for treatment and prevention
  - Test whether mobile devices can encourage healthy behaviors
  - Lay scientific foundation for precision medicine for many diseases

Follow the Initiative’s progress and consider volunteering for this landmark effort.

www.nih.gov/precisionmedicine
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www.nih.gov/precisionmedicine
Precision Medicine Initiative Summit
White House, President Obama, 2/25/2016

• White House Announces UA's Involvement in National Precision Medicine Initiative
  https://uanews.arizona.edu/story/white-house-announces-ua-s-involvement-in-national-precision-medicine-initiative

• As part of its statewide programs, UAHS is launching three new precision medicine initiatives:
  – System-wide dissemination of an on-demand "case-based reasoning" system that intelligently searches and analyzes entire databases of electronic medical records. This will give clinicians the power to develop an individualized and effective treatment plan for unusual or complex clinical conditions, grounded on practice-based evidence.
  – Development of genetic assays to predict an individual's response to therapy and prevention of adverse reactions, termed "pharmacogenomics".
  – Partnership with five other institutions to advance the Sanford Pediatric Genomics Consortium to help families and their providers improve health-care decision-making through better understanding and integration of genomic evidence.
Simpler transcriptome information theoretic framework

Lussier YA, Chen JL. The Emergence of Genome-Based Drug Sci Transl Med. 2011 17;3(96)

Complexity of Individual Genomes

3.0–3.5 million base pairs & 1,000 CNVs = 1 individual:

• fraternal twins with childhood-onset dystonia:
  o 2.50 million and 2.42 million SNPs in each,
  o twins shared 1.63 million SNPs
  o 1 million unique for each one is expected.

• A pair of homologous chromosomes in a given individual are ~99.5% identical in total number of base pairs,
  o in contrast to the assumption that any two human individuals are 99.99% identical at the DNA level

• Individual genome: 20,000–25,000 coding variants
  o 9,000–11,000 are non-synonymous
  o ~10,000 private variants not found in hapmap or 1000 genomes

Frequency of Somatic Mutations in Various Types of Human Cancers

Gastric cancer: **3.5 million somatic mutations** (100 tumors matched with normal)

Liver cancer: **4,886–24,147 somatic mutations per tumor**, with the average number of somatic point mutations at the whole-genome level: 4.2 per megabase.

Chronic lymphocytic leukaemia: **About 1,000 somatic mutations** per tumor.

Malignant melanoma (COLO-829 cell line): **33,345 somatic mutations**

One Small-cell lung cancer, **22,910 somatic mutations**

Older study to estimate the frequency of somatic mutations:
lung carcinomas (4.21 per Mb), followed by gastric cancers (2.10 per Mb, the highest prevalence of somatic mutations), ovarian cancers (1.85 per Mb), colorectal cancers (1.21 per Mb) and renal cancers (0.74 per Mb).
Single Markers vs multi-gene mechanisms
Scalar theory & diseases of molecular pathway deregulation

- Pathway deregulation ➔ Diseases with **different genetic causes**
  - e.g. Hemophilias can be inherited or acquired
Nonsense and missense mutations in hemophilia A*
Disruption of the Metabolic Pathways of Inherited Coagulopathies

copyright 1996 M.W. King
Summative regulation of bleeding time trait

*Acquired (environmental) Coagulopathies*: decrease expression of many genes without mutations

Coagulopathy secondary to chronic liver disease (e.g. cirrhosis)
Summative effect of diverse genetics = similar transcriptome

Pathway (KEGG)

Genetic (OMIM)

Disease (SNOMED)

Sematics (SNOMED)

Clinical system (SNOMED)

Factor VII deficiency (disorder) 37193007

Hereditary factor XI deficiency disease (disorder) 49762007

Afbrinogenemia (disorder) 278504009

227500 + F7 F7 DEFICIENCY

281833003 Hematological system (body structure)

264900 + F11 F11 DEFICIENCY

281833003 Hematological system (body structure)

134820 + FIBRINOGEN, A ALPHA POLYPEPTIDE

202400 # Fibrinogen AFIBRINOGENIMIA, CONGENITAL

134830 + FIBRINOGEN, B BETA POLYPEPTIDE

is a
Transcriptome analysis

Cohort

Case
Control

Gene Expression

Paired samples

Common Gene / pathway signature

Individual

Control / Case Paired samples

Gene Expression

Common Pathway signature

Individual Pathway signature

Transcriptome analysis
N-of-1-\emph{pathways} Mahalanobis Distance (MD)
N-of-1-*pathways* Mahalanobis Distance (MD)

**Dynamic Expression**

Control

Case

**Pathway Reduction**

**Deviations from Equality**

![Diagram showing N-of-1-pathways Mahalanobis Distance (MD)]
N-of-1-pathway: 2) comparison tool

- Patient Count: #Patient sharing each deregulate GO-BP Term
Patient individual comparison to external GS

Ratio of the deregulated GO-BP Terms linked to GS
GAP:
symbolic formalism for computer-assisted human interpretation

Simplify via
- Transform
- Projection to transcriptome “space”
"N-of-1-pathways" unveils personal deregulated mechanisms from a single pair of RNA-Seq samples: towards precision medicine

Vincent Gardeux, Ikbel Achour, Mark Maienschein-Cline, Gurunadh Parinandi, Lorenzo Pesce, Jianrong Li, Neil Bahroos, Haiquan Li, Ian Foster, Joe G.N. Garcia, (Robert Win), Yves A. Lussier

**Problem:** Accurately predicting the biologic and statistical significance of the deregulation of a pathway from one normal tissue and one cancer tissue of an individual patient’s transcriptome rather than genome.

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**Disease-free survival > 5yr**

TCGA-38-4626

TCGA-55-6986

TCGA-44-6776

TCGA-55-6983

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**Death of disease < 1yr**

TCGA-50-6595

TCGA-55-6975

TCGA-55-6978

TCGA-55-6979

TCGA lung adenocarcinoma dataset
Study of \textit{ex vivo} vs \textit{in vivo} response to rhinovirus from PBMC (Peripheral Blood Mononuclear Cells)
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