UNITED STATES
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A Look at Personalized Medicine

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Overview

- What is personalized medicine?
- Genetic mapping and SNPs
- The diagnostic industry
- Public policy
- Pharmacogenetics
- Case study – warfarin
- Sample claims relating to personalized medicine

A Definition of Personalized Medicine

Personalized medicine is the use of information from a patient's genotype to:

- initiate a preventative measure against the development of a disease or condition, or
- select the most appropriate therapy for a disease or condition

that is particularly suited to that patient.

Definition paraphrased from www.wikipedia.org

Other sources: Jones, D. *Nature Reviews Drug Discovery* 2007; 6:770-771; Katsanis et al. *Science* 2008; 320(5872):53-54; Feero et al. *JAMA* 2008; 299(11):1351-1352

Human Genome Research

Human Genome Project in 2003

Finishing the euchromatic sequence of the human genome.
Nature 2004; 431 (7011): 931-945.

Phase I HapMap project in 2005

A haplotype map of the human genome.
Nature 2005: 437(7063):1299-1320

Encyclopedia of DNA Elements (ENCODE) project in 2007

Identification and analysis of functional elements in 1%
of the human genome by the ENCODE pilot project.
Nature 2007; 447(7146):799-816

1000 Genomes Project in 2008

DNA sequences. A plan to capture human diversity in 1000 genomes.
Science 2008; 319(5863):395

Source: U.S. DOE (www.genomics.energy.gov), Human Genome Project Information

Genotypes and Human Disease

- Do all humans have the same DNA?
- What are single nucleotide polymorphisms or SNPs?
- Can we associate SNPs with medical histories of individuals and achieve statistically significant correlations?

The Diagnostic Industry

Companies are currently marketing test kits.

Saliva samples are tested and reports are sent to the consumer.

Reports are based accepted clinical genetic associations with risk but can also be obtained for research without demonstrated association with risk.

The Debate on Direct-to-Consumer Tests

Pros

- Early warning about predisposition could promote healthier lifestyles
- Better patient confidentiality

Cons

- Commercialization – is testing really necessary?
- Lacks regulation that would ensure accurate risk assessments
- Is the data more harmful than helpful without context?
- Is it beneficial to be informed that you are at high risk to develop a disease for which there is no cure?
- Testing of third parties and their privacy

Source: Howard et al. *Future Medicine* 2008; 5(4):317-320

Public Policy and Personalized Medicine

Genetic Information Nondiscrimination Act of 2008 (H.R. 493, S.358)

Senator (now President-elect) Barack Obama's *Genomics and Personalized Medicine Act of 2007* (S.976)

DHHS Secretary's Advisory Committee on Genetics Health and Society (SACGHS)

Sources: www.govtrack.us and Qureshi et al. *Future Medicine* 2008; 5(4):311-316

A Definition of Pharmacogenetics

Pharmacogenetics (PGx) is the science of how an individual's genotype affects their body's response to drugs.

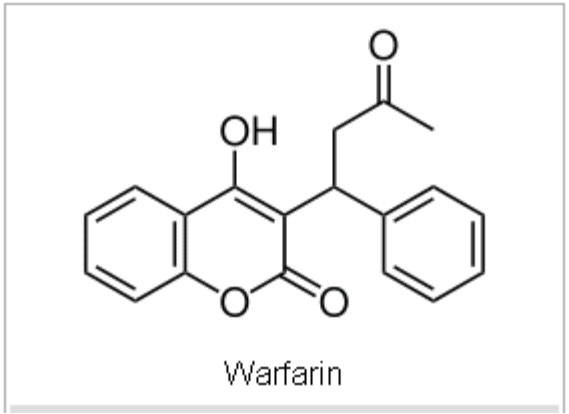
Definition paraphrased from www.wikipedia.org

Examples of SNPs Linked to Drug Response

Gene Symbol	Description	SNPs	Clinical Phenotype
CYP2C9	Cytochrome P450 2C9	multiple	variable metabolism of CYP substrates in the liver
TPMT	thiopurine methyl transferase	multiple	hematopoietic thiopurine toxicity
UGTIAI	UDP-glcyosyl transferase IAI	multiple, in promoter & encoding regions	UGTIAI*28 variants associated with increased irinotecan toxicity
VKORC1	vitamin K epoxide reductase complex I	multiple, i.e. 1639G>A in promoter	variable anticoagulant effect of warfarin
t(9,22) translocation	t(9,22) BCR-ABL translocation	translocation	Gleevee (imatinib) effective against chronic myeloid leukemia with translocation
ERBB2	ERBB2, HER/Neu	overexpression of protein	Herceptin for breast cancer with ERBB2 overexpression
EGFR	epidermal growth factor receptor	exon 18-21 mutations	human lung cancers with mutations response better for Iressa (gefitinib)

Source: Human Molecular Genetics, 14(2): R207-R214 (2005)

Case Study: Warfarin



Warfarin

- Most widely prescribed oral anticoagulant for preventing thrombolytic events, despite its narrow therapeutic range
- Problematic dosing due to patient's diet, age, and other medications
- Second most common drug implicated in adverse drug reaction-linked emergency room visits

Sources: US FDA (www.fda.gov), Warfarin Information; Rettie et al. *Molecular Interventions* 2006; 6(4):223-227; Flockhart et al. *Genetics in Medicine* 2008; 10(2):139-150

Personalized Warfarin Dosing

- One-third of thrombosis patients metabolize their warfarin dose differently than expected due in large part to variations of 2 genes,*VKORC1* and *CYP2C9*
- *VKORC1* SNPs, such as the 1639G>A allele, indicate that a patient will respond well to a lower dose of warfarin
- CYP2C9*2 and CYP2C9*3 alleles encode SNP variants of CYP2C9 with reduced efficiency in degrading warfarin
- Warfarin labeling suggesting genetic testing of *VKORC1* and *CYP2C9* is the first indication of personalized dosing being approved by the FDA

Intellectual Property Rights and Personalized Medicine

- Claims drawn to methods of treatment based on genetic information (SNPs) of an individual using suitable dosages of medications
- Claims drawn to isolated SNPs in DNA
- Claims drawn to methods of treatment of diseases based on genetic information (SNPs) of an individual using correlations of particular SNPs

Example 1: Pharmacogenetics Claim

1. A method of treating a human subject having a thrombosis with a dosage of warfarin, said method comprising:

a) obtaining a nucleic acid sample from said human subject;

b) subjecting the sample to PCR and identifying i and/or ii:

i) in the subject's *VKORC1* gene, the nucleotide base at position X of SEQ ID NO:1 in the sample from the subject and/or

ii) in the subject's *CYP2C9* gene, the nucleotide base at position Y of SEQ ID NO:2 in the sample from the subject; and

c) treating the human subject with a dosage of warfarin indicated by their genotype as identified in b.

Example 2: SNP Claim

2. An isolated nucleic acid sequence comprising SEQ ID NO:1.

The specification teaches that SEQ ID NO:1 is a variant of the *ERBB2* gene having an A (adenine) to C (cytosine) mutation at position 101 (A101>C).

*this mutation (A101>C) is typically found in breast cancer patients.

*this mutation (A101>C) correlates with a significantly better response to "breast cancer drug X" versus placebo.

*without mutation (A101>C), "breast cancer drug X" is an ineffective treatment.

Example 3: Methods Correlating SNPs and Diseases

3. A method for determining whether a human subject having breast cancer will be effectively treated with "breast cancer drug X", said method comprising:

a) considering data in a database comprising genetic patient information about the *ERBB2* gene at position 101 of SEQ ID NO:1; and

b) correlating the presence of a cytosine at position 101 of SEQ ID NO:1 with effective treatment of the human subject with "breast cancer drug X".

Neither tied to a machine/apparatus nor performing a transformation, therefore, does not meet the requirements for 35 USC 101

Example 4: Methods of Treating Diseases that Correlate with SNPs

4. A method for treating a human subject having breast cancer, said method comprising:

a) obtaining a nucleic acid sample from said human subject;

b) subjecting the sample to PCR and identifying the nucleotide present at position 101 of SEQ ID NO:1; and

c) treating the human subject with "breast cancer drug X" when a cytosine is detected at position 101 of SEQ ID NO:1.

Example 5: Enabling Methods of Treating Diseases that Correlate with SNPs

5. A method for treating a human subject having breast cancer, said method comprising:

a) obtaining a nucleic acid sample from said human subject;

b) subjecting the sample to PCR and identifying the nucleotide present at position 101 of SEQ ID NO:1; and

c) treating the human subject with "breast cancer drug X" when a cytosine is detected at position 101 of SEQ ID NO:1.

The specification teaches that SEQ ID NO:1 is a variant of the *ERBB2* gene having an A (adenine) to C (cytosine) mutation at position 101 (A101>C).

*this mutation (A101>C) is typically found in breast cancer patients.

*this mutation (A101>C) correlates with a significantly better response to "breast cancer drug X" versus placebo.

*without mutation (A101>C), "breast cancer drug X" is an ineffective treatment.

Further, the specification did not distinguish among patient populations tested.

Example 5 (con't): Enabling Methods of Treating Diseases that Correlate with SNPs

Prior art teaches that variability in treatment responses among patient populations may be an ***unpredictable*** factor in SNP correlation studies.

Post-filing date art teaches:

*Patient population A and patient population B subjects follow the correlation disclosed in the specification

*But no correlation found in patient population C subjects having the *ERBB2* gene A101>C mutation (i.e., Patient population C subjects responded similarly to "breast cancer drug X" and placebo demonstrating that "breast cancer drug X" is ineffective for this population).

The post-filing date art shows evidence that the instant method is not effective for treating patient population C with breast cancer. The appropriateness of making any enablement rejection should be considered based on the foregoing facts.

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