

## Patenting Personalized Medicine

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## ABSTRACT

This article discusses the patentable subject matter and timing of filing patent applications on the discoveries in the emerging field of personalized medicine.

## INTRODUCTION

Personalized medicine, which broadly speaking includes pharmacogenetics, pharmacogenomics, pharmacoproteomics, and nutrigenomics is one of the most exciting areas of science emerging in the wake of sequencing the human genome. It has long been known that different individuals react to the same drug or nutrient differently—and there would be a lot to gain in matching the right therapy with the right individual. A recent report in the journal of Science put a number on current sales of pharmacogenomic therapies by the pharmaceutical industry to \$3.65 billion, compared to the total pharmaceutical market of \$550 billion.<sup>1</sup> While sales of personalized medicine presently represent just a fraction of the total market of pharmaceuticals and personalized medicine is just beginning to win support in the medical and pharmaceutical community, the products based on personalized medicine are expected to be part of the mainstream medical practice within 10 years.<sup>2</sup>

Patents provide time limited protection to inventions allowing inventors to reap some financial benefit from their hard work and encouraging the development of new and improved therapies. This review highlights some specific points regarding patentable subject matter as well as the

ripeness of inventions in the area of personalized medicine. Specifically, this report will answer the following questions: What types of discoveries could be protected by patents? When is a discovery ripe for patenting?

## WHAT TYPES OF PERSONALIZED MEDICINE DISCOVERIES ARE PATENTABLE?

The theme of personalized medicine is that “one size does not fit all.” However, this does not necessarily mean that each individual needs a drug of their own, or a “tailor-made” fit. One can think of personalized medicine like buying clothing—you have to know about how tall and heavy you are to select from small, medium, and large jogging pants to find the closest fit. The more accurate the size the better the garment fits you. One can also use such “scales” to allow improved targeting of drugs and therapies. The scales based on one or a few genotypic markers and their association with drug effect or metabolism may give one a better drug “fit” than a therapy given without any knowledge of the response of the recipient.

Defining the scales is tricky. This opens a door to an important aspect of potential patentable subject matter: “scales”, or teaching one how to select the most desirable target patient for a specific therapy. Patents can provide

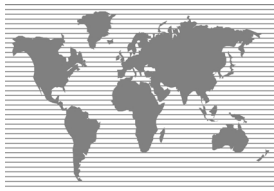
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one way of protecting these “scales” whether they are a custom fit, divide the population in two groups, i.e. responders and non-responders, or they divide the population in more than two groups, such as slow, medium, and high metabolizers. For example, patent protection can be aimed at methods of identifying individuals who are most responsive or least responsive to a certain therapy. A recent U.S. FDA approved medicine, BiDil, to treat heart failure in African Americans is an example of limiting the use of a drug to only the most responsive population.

Such screening methods could provide a first step to doctors when they select a right therapy for a patient or a group of patients most likely to benefit from the drug. Moreover, once the doctor has identified the right therapy, the same or a different genetic profile can further help to determine the most likely effective dose. The scale can also separate people in groups based on harmful side effects. For example, already today, doctors screen for rare gene mutations in children affected with acute lymphocytic leukemia (ALL) to avoid giving a drug, 6-mercaptopurine (6-MP), to patients who cannot metabolize it.<sup>3</sup> Such precaution saves lives. Individuals who metabolize 6-MP poorly often encounter fatal consequences from the treatment which is effective in 299 of 300 patients.

The patentable subject matter in scales can be based on a variety of analyses. One analysis provides for identification of specific genetic allele variants, or polymorphisms, resulting in functional differences in the functional regions of the genes, such as coding regions, promoter, enhancer or silencer regions that result in differences in the drug response through effects on the quality or quantity of the drug's target protein. One can screen for the different polymorphisms in the target gene or protein, and determine how they affect the response to the drug if the target of the drug is known, and the mechanism of the drug action is known. Both the functional polymorphisms themselves and the method of treating a patient carrying the specific allele variant with the drug can be claimed. However, even if the polymorphism was previously known, its association with a certain drug response may still be novel and non-obvious and thus potentially patentable. The patentable subject matter of a scale can also be based on individual's responsiveness to a drug or treatment based on a combination of allele variants of more than one gene.

An example of matching the right patient with the right drug is the recent identification of specific mutations in the epidermal growth factor receptor, EGFR, gene by investigators at Massachusetts General Hospital and Dana Farber Cancer Institute.<sup>4</sup> These mutations render individuals affected with non-small cell lung carcinoma and carrying

the mutations more likely to respond to drugs like Iressa, manufactured by AstraZeneca PLC, and Tarceva, made by OSI Pharmaceuticals. Both Iressa and Tarceva are effective in about 10% of the patients with this type of cancer. The genetic screening test now under development by Genzyme, would allow giving these drugs only to the most responsive patients.<sup>5</sup>

Such genetic makeup can also lead to potentially patentable scales for determining drug dosages for a particular individual. For example, enzymes belonging to cytochrome P450 (CYP450) superfamily take part in metabolizing drugs, toxins and other foreign substances entering the body. Roche Diagnostics has recently developed a genetic test, the AmpliChip CYP450 Test, which combines genotyping with an interpretation table that allows classification of people into groups of slow, medium, high and ultrahigh metabolizers of certain drug families. These “predictive phenotypes” have the potential to help doctors to prescribe right doses of drugs known to be metabolized by these selected members of CYP450 family of enzymes.<sup>6</sup>

Another way of defining patentable subject matter of a scale is identification of haplotypes, a combination multiple

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genetically associated nucleic acid polymorphisms or alleles, that are inherited as a physically linked block, that are associated with a responsive or non-responsive phenotype. This approach can be used, when the specific target or mechanism of action is not necessarily known but people with certain regional allele combination appear to respond better

or worse to a therapy. Haplotypes are usually compiled using known polymorphic markers, and thus the polymorphisms themselves are not patentable. However, the combination of polymorphisms that are associated with a certain phenotype, e.g. responsiveness to a therapy or development of an adverse reaction when exposed to a drug, could be subject matter for a patentable scale.

For example, scientists led by Dr. Ordovas at Tufts University, Boston, discovered that a combination of certain polymorphisms in the genetic locus of perilipin, allow for the determination of a high or low risk of developing obesity.<sup>7,8</sup> The perilipin gene determines how much perilipin protein is produced and perilipin protein, in turn, controls the breakdown of fat within the cell. More perilipin means more fat is stored in the cells. Although the polymorphisms themselves are known, and functional effects of these perilipin alleles are still unknown, the statistical analysis of genotypic and phenotypic data has allowed identification of genetic patterns that can be protected in association with the phenotypes.

Allele variant combinations of genes that are located in different chromosomes and that affect formation of a spe-

cific phenotype can also provide potentially patentable subject matter. The allele combinations may be associated with more severe disease and consequently can affect the treatment decisions. For example, such gene groups and the specific risk-allele combinations have been identified by Boston University and Children's Hospital scientists in sickle cell anemia patients with an increased risk of overt stroke.<sup>9</sup> It is known that patients with sickle cell anemia have an increased risk of overt stroke, which can be prevented if the individual at risk receives preventive therapy. However, not all patients with sickle cell anemia have a stroke. Identification of individuals at highest risk of developing a stroke allows targeting prevention strategies to this sub-group of sickle cell anemia patients. Such targeting could result in better patient compliance with the therapy and significant cost savings.


Identification of gene expression patterns that measure responses of a variety of genes to a specific therapy is yet another way of providing scale with potentially patentable subject matter. The expression patterns provide scales that can be simple on/off scales, i.e., the gene either is or is not expressed. The scales can also have any number of shades of grey representing, for example, low, medium or high expression. Computer analysis of the gene expression patterns in numerous individuals exposed to the same environmental change, such as receipt of a drug, provides a way of identifying the scales. The gene expression scales that are presented using gradients likely require a teaching of how to measure the expression, what the target cell or tissue is, and sometimes what the gender or age of the patient is. However, once a group of genes has been found to be expressed a certain way in response to a certain environmental change, whether it be illness or therapy, a scale can be drawn. This scale provides a group of genes, whose expression pattern in association with a disease or therapy can be patented. Cancer classification assays are a classic example of this type of scale.<sup>10</sup> A group at Boston University, lead by Drs. Jerome Brody and Avi Spira, has identified gene expression changes in a lung epithelial cell transcriptome in response to cigarette smoke and concluded that certain smokers are more prone to develop lung cancer than others.<sup>11</sup>

## WHEN IS PERSONALIZED MEDICINE DISCOVERY RIPE FOR PATENT FILING?

The time to file a patent application is the time when you realize that the discovery can be useful in identifying a subset of patients. The massive screening of disease-associated, metabolism associated, or drug response-associated genetic variants using a variety of statistical analysis methods may provide a bewildering amount of information. A scientist may see a population divide first into two groups, then into three, four or more groups depending on the number of genetic markers analyzed and the number of people screened. The time to file is when a researcher sees and realizes formation of the first division or scale in the study material. The screening may eventually lead, for example, to tailor-made therapies for very specific genotypes. When the additional scales evolve, further applications may be filed. However, even the first division may provide a crucial step in helping patients to receive better treatment. Filing should be considered before public discussion about the discovery, whether it be a published article or a poster at a meeting.

The iterative process of filing a number of patent applications can be made relatively inexpensive at the beginning by filing of provisional applications.<sup>12</sup> A decision can later be made at the time of filing the utility applications, whether to combine the applications into one or keep the applications separate or even abandon the applications that upon further research proved potentially commercially uninteresting.

## SUMMARY

Personalized medicine promises to have a profound effect on the future of pharmaceutical interventions. As with any emerging technology, patent protection is critical to commercialization. Personalized medicine is no exception. Keeping an eye on research and filing for patent protection when the first scale or division in a study is recognized and filing additional applications as other discoveries are made will ensure that sufficient protection is obtained to promote commercialization of discoveries in the field of personalized medicine. 

### ENDNOTES

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10. See, for example, U.S. Patent application No. 20050095607.
11. A. Spira et al., *Effects of cigarette smoke on the human airway epithelial cell transcriptome*, 101(27) PROC NATL ACAD SCI U S A 10143, 10143-10148 (2004).
12. The U.S. patent law provides for filing of provisional patent applications. These applications will not be examined and will lapse after 12 months from the filing date, unless they are converted into the "regular", so called utility applications. The filing of the utility patent application that wishes to claim the benefit of the filing date of the provisional application must occur within the 12 month period from filing the provisional application.