

Genomas, Inc.

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Genomas, Inc.

Genomas, Inc. is developing novel diagnostic products to personalize disease prevention and health enhancement. The company's proprietary PhysioGenomics™ technology allows it to rapidly and precisely produce 'PhysioTypes™'. PhysioTypes are predictors of response to diet, exercise, and drugs (not diagnostics for disease) and are utilized to direct preventive strategies. A PhysioType is made from the combination of all genetic, physiological or clinical markers that Genomas has discovered to be significant determinants of individual response. PhysioTypes are revolutionary healthcare products that empower physicians with the unprecedented capability to prescribe personalized and highly effective preventive treatments, incorporating diet, exercise and drug regimens for each patient. Genomas conducts clinical research with major clinical institutions to discover these PhysioTypes with plans to commercialize them to practicing physicians and hospitals.

The initial product development focus of Genomas, Inc. is obesity and metabolic syndrome. Metabolic syndrome is a premorbid condition diagnosed by central obesity, imbalances in lipids, elevated blood pressure, and glucose intolerance. It is the predecessor to the dire consequences of diabetes, cardiovascular disease, and end-stage organ damage. Two-thirds of the American population is either obese or overweight and a third of the adult population has metabolic syndrome. Prevention of metabolic syndrome and diabetes is now a major public health imperative recognized by Fortune 500 companies as a threat to their competitiveness. Major sectors of healthcare are concentrated in this disease area, including the US\$10 billion cholesterol drug market, the US\$4 billion diet market, and the US\$2 billion fitness and sports sectors. The alarm surrounding obesity will introduce a new market for the management and prevention of this disease and interventional strategies previously unseen in medicine. The demographic sector driving this opportunity is the affluent and educated 45- to 65-year-old 'baby boomer' cohort with metabolic syndrome who are seeking preventive treatment to arrest its course to diabetes or cardiovascular disease.

PhysioGenomics™ is a proprietary technology based on systems biology, which rapidly analyzes multiple genes and baseline determinants of environmental responses for an individual. This technology unravels pre-existing genetic (inherited DNA variability) and physiological determinants of response to each intervention, be it

exercise, diet, or drug. With this technology, the company has already discovered PhysioTypes™ of exercise and diet for the preventive treatment of these conditions. Genomas is also pursuing the safety of drug prescription. The company has entered into a strategic alliance with Illumina, Inc., (San Diego, CA, USA), to deploy this technology on metabolic syndrome.

Genomas will market its proprietary PhysioTypes to physicians and hospitals and has created a business unit for the immediate deployment of PhysioTypes and drug metabolic markers into the medical marketplace, the Laboratory of Personalized Health (LPH), which supports their clinical use. The company's prevention focus allows effective and multi-pronged intervention in the disease process and avoidance of drug side effects, which complicate treatment. Through its discovery efforts, Genomas is perfecting PhysioGenomics, with plans to contract this technology with managed care, nutrition, fitness, pharmaceutical and diagnostic companies for its application in specific settings relevant to the customer. These applications include disease management, optimized diet development, personalized fitness, and prevention of drug side effects. While doing so, the company pursues proprietary research in metabolic syndrome and obesity to develop its internal product pipeline.

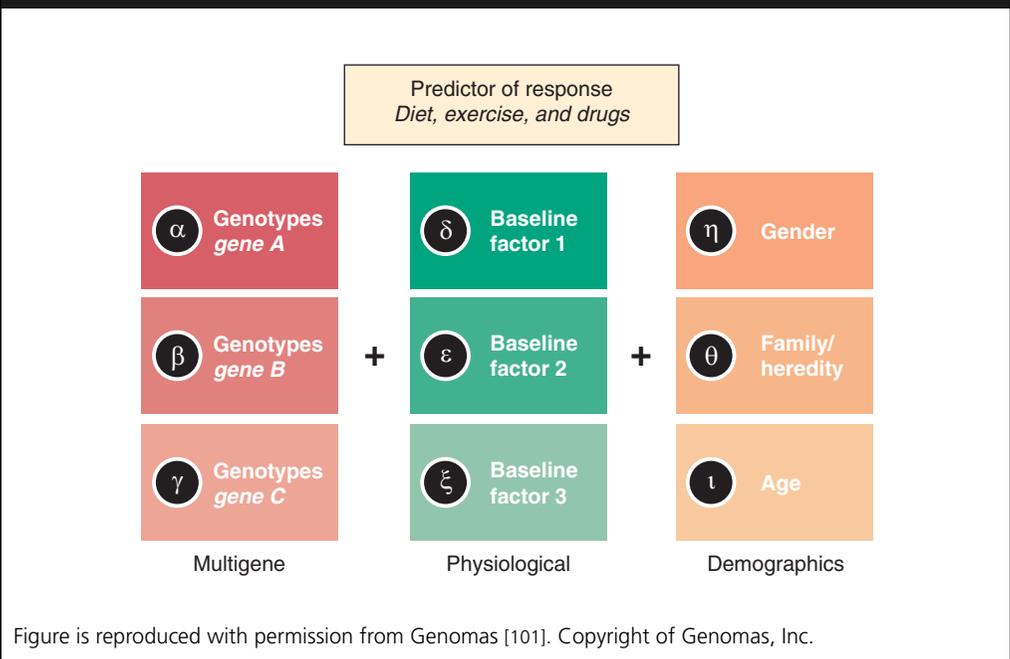
Genomas PhysioType™ products

The precision in prediction afforded by the PhysioType is due to the product's information content. The PhysioType is multi-modular and integrates data from several sites of DNA varia-

Keywords: diabetes, metabolic syndrome, obesity, PhysioGenomics™, PhysioTypes™

**future
medicine**

Figure 1. What is PhysioType?

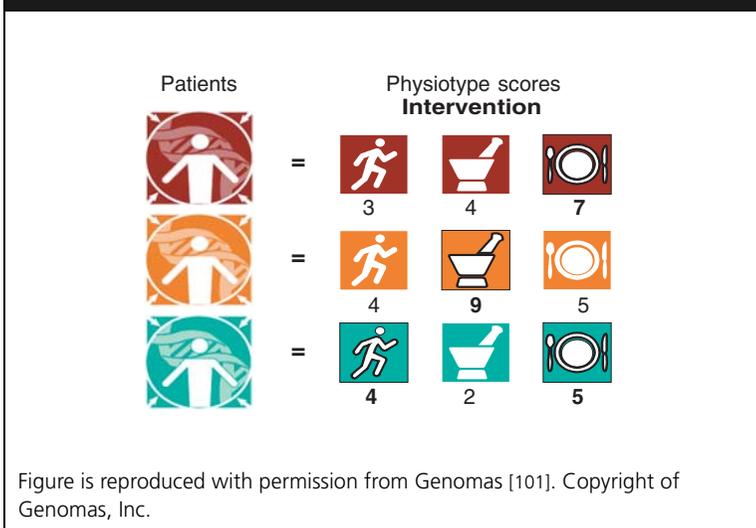


tion (genotypes of multiple genes), from presenting baseline physiological and clinical information (physical exam and diagnostic workup), and from demographics (gender, age, medical history)(Figure 1). The purpose of PhysioType is to predict responses to diet, exercise, and drug treatments, and to select the best treatment for the patient from these options. The PhysioType is a novel product in healthcare for guiding treatment based on the unique integration of existing modes of medical management with genetic information on treatment responses. In a fundamental way, the PhysioType seamlessly combines ‘nurture’ (how the patient presents in middle age with decades worth of environmental, cultural and lifestyle influences on his or her own health) with ‘nature’ (the patient’s genetic constitution inherited at birth).

The PhysioType is neither a diagnostic of disease nor a ‘genetic screen’ for disease susceptibility. The use of genetic markers in medicine has been relegated to inherited diseases where DNA mutations induce such magnitude of effects as to be fully predictive of the medical course. For gene–environment interactions, this approach has not been successful as any single DNA variation is only partially predictive, and even then, the prediction requires information on the baseline function. The research of Genomas and its principal founder Dr Gualberto Ruano, has led the company to develop its PhysioGenomics technology to address gene–environment interactions relevant

to treatment outcomes. PhysioGenomics utilizes physiology to characterize the presenting condition of the individual, and genomics to characterize the environmental responses.

PhysioTypes are discovered for various treatments and used for decision support in a menu-driven format. For achieving a desired therapeutic outcome for a given patient, PhysioTypes for each of the various treatment alternatives (exercise, drugs, and diet) are applied to quantitatively predict the patient’s response to each. To derive the PhysioTypes, Genomas will incorporate several physiological and clinical data gathered by the physician and genomic data from several gene haplotypes gathered at the Company. Predictions made by the PhysioType will rank the best alternatives among the menu options to achieve a desired goal. In Figure 2, the choices are to recommend a given kind of exercise, drug or diet regimen. If one of the options is high scoring, it can be used on its own. Thus, in the example, diet is high scoring in the first patient, and a drug in the second. If the options are midrange, they can be used in combination, as is the case in the third patient, where exercise and diet will each have a positive effect but are unlikely to be sufficient independently. If none of the options is high or at least mid scoring, the PhysioType analysis suggests that the patient requires another option not yet in the menu. As more options are built into the menu, the greater the chance that all patients will be served at

Figure 2. Personalized healthcare by customizing intervention.

increased precision of intervention and with optimal outcome.

As long as the appropriate PhysioGenomics research has been performed for each intervention in the menu, an individual's PhysiTypes would evaluate all possibilities for optimized healthcare. The clinician can query for simple indices, such as raising high-density lipoprotein (HDL) or lowering triglycerides, or compounded indices, such as low-density lipoprotein (LDL)/HDL ratios or simultaneous elevation of HDL and reduction of triglycerides. PhysiTypes are derived for the combined outcome, and the same decision-making process can proceed seamlessly.

Genomas PhysioGenomics™ technology

In our research programs, we aim to create models that predict various lipid, inflammatory and anthropometric responses to diet, exercise, and drugs. Generation of these PhysiTypes for these therapeutic modes is viable because of the throughput and precision of our PhysioGenomics technology. A typical research study requires only 250 individuals similarly exposed to diet, exercise, or drugs, and can be completed in only 6–9 months. To achieve this goal, the company will engage in clinical research collaborations with major medical centers, and acquires exclusive commercial rights on any markers of response derived from such studies. We estimate the cost of each program comprised of a discovery phase and a validation phase to be US\$250,000, some of which will be deferred by pending Small Business Innovation Research (SBIR) grants. Genomas has already secured a

research grant for its exercise program from Hartford Hospital (CT, USA), where the baseline physiological and clinical level is measured for several phenotypes, ranging from serology, physical exam, imaging, endocrine function, or genomic/proteomic markers. The response of each individual in the same phenotypes determined at presentation is then acquired after the specified treatment or intervention. PhysioGenomics utilizes the variability in response within the cohort to derive the predictors of response. After the PhysiTypes have been established from the research cohort for a given intervention, they can be applied to predict the response of a new individual to the intervention in a separate validation study. If validated, the PhysiType is ready for clinical use.

The medical utility of our product will depend on the range of options it can customize. Within each of the major treatment modes (exercise, drug, and diet), alternatives should be available to achieve specified goals. For example, consider dietary intervention to raise HDL in a patient with metabolic syndrome, and a decision on whether to proceed with a low fat or low carbohydrate diet. With PhysiTypes discovered each for low fat and low carbohydrate diets, predictions can be drawn for an individual's response to either. The person's physiological and genetic markers would be entered into the PhysiTypes, and the best diet based on the PhysiType's prediction can be identified for the individual. Genomas will generate PhysiTypes not only for various kinds of diet, but also for various kinds of exercise and drug treatments. The menu of possible interventions is thus broadened. The PhysiType yielding the best outcome for a given desired effect guides the mode of intervention from an increasingly diversified menu, thus allowing enhanced personalization and customization of treatment.

Healthcare opportunity: obesity, diabetes, and metabolic syndrome

Approximately two-thirds of the US adult population is overweight or obese (approximately one-third are considered obese) with an annual total economic cost exceeding US\$117 billion of which the estimated annual medical expense exceeds US\$92 billion or more than 9% of USA health expenditures. This can be directly attributed to the fact that excess weight accounts for an estimated 70% of the diabetes risk in the US, a nearly threefold risk in the prevalence of high blood pressure and a nearly twofold risk in the

Figure 3. Metabolic syndrome.

Metabolic syndrome is formally defined as having three or more of the following abnormalities:

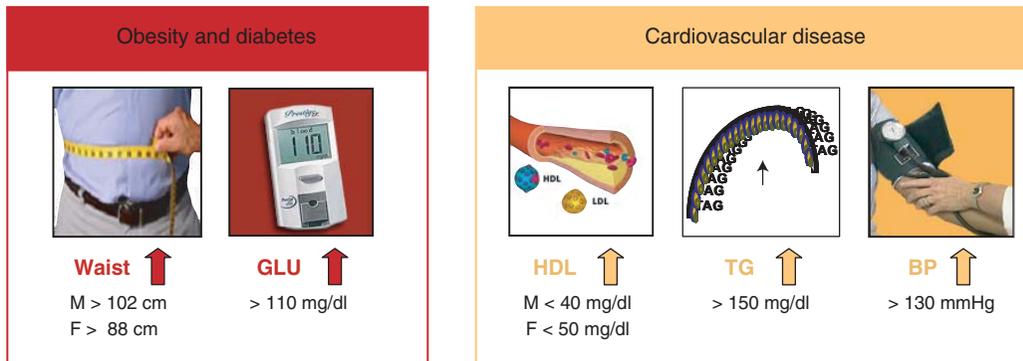


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 BP: Blood pressure; F: Female; GLU: Glucose; HDL: High-density lipoprotein; M: Male; TG: Triglycerides.

prevalence of high blood cholesterol. Obese individuals have a 50–100% increased risk of death from all health-related causes (primarily cardiovascular), compared with normal-weight individuals. Obese individuals have 30–50% more chronic medical problems than those who smoke or drink heavily. The seriousness of these problems is indicated by concerns that obesity may, in fact, obliterate 30 years of progress in the reduction of morbidity and mortality related to cardiovascular disease.

Metabolic syndrome is a prevalent and serious disease of relatively recent recognition by the medical profession. Previously known as ‘Syndrome X’, metabolic syndrome (MetSyn) was formally defined in the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults [1]. In terms of disease progression, it represents an intermediate step between obesity and diabetes, but significantly overlaps both conditions. Metabolic syndrome is formally defined as having three or more of the following abnormalities (Figure 3):

- large waist circumference
- elevated serum triglycerides
- depressed HDL
- elevated blood pressure
- elevated serum glucose

Clearly, it reflects a multi-system disease with severe implications for cardiovascular health.

A recent study from the US Centers for Disease Control published in the *Journal of the American Medical Association*, estimated the prevalence of metabolic syndrome to be 20–25% in the 40–49 years of age cohort, 33% in the 50–59 year range, and 40–45% in the 60–69 year range [2]. This report states, ‘While proper management of the individual abnormalities of this syndrome can reduce morbidity and mortality, it seems unlikely that management of the individual abnormalities of this syndrome provides better outcomes than a more integrated strategy.’ [2]. Further, it concludes ‘Because the root causes of the metabolic syndrome for the overwhelming majority of patients are improper nutrition and inadequate physical activity, the high prevalence of this syndrome underscores the urgent need to develop comprehensive efforts directed at controlling the obesity epidemic and improving the physical activity levels in the United States.’ [2].

Health promotion and prevention that include screenings and education should be a top priority for providers; yet, time constraints, limited formal training in nutrition and nutritional counseling, and lack of reimbursement have stagnated preventive efforts with diet and exercise. Metabolic syndrome itself is a new disease indication without standardized pharmacotherapy. There is a clear need for new standards and options for the treatment of metabolic syndrome with exercise, diet, and drugs.

Highlights

- PhysioTypes are predictors of response to diet, exercise, and drugs (not diagnostics for disease) and are utilized to direct preventive strategies.
- PhysioGenomics is a proprietary technology based on systems biology, which rapidly analyzes multiple genes and baseline determinants of environmental responses for an individual.
- Genomas will market its proprietary PhysioTypes to physicians and hospitals and has created a business unit for the immediate deployment of PhysioTypes and drug metabolic markers into the medical marketplace, the LPH, which supports their clinical use.

Outlook: what the future holds for Genomas

Genomas will commercialize its PhysioGenomics technology and PhysioTypes through various channels with differing time horizons.

Near term

In 2004, Genomas will establish its LPH, a fully certified clinical laboratory under CLIA (Clinical Laboratory Improvement Act of 1988), for the near-term commercialization of PhysioTypes and drug metabolism markers. The initial testing will most likely be for psychiatric drugs. The LPH services include testing of licensed or public domain gene markers and testing of proprietary PhysioTypes.

The company will also be providing support services to the Institute of Living, Hartford Hospital and physicians for various genetic markers of clinical relevance. Such markers include drug metabolism, effectiveness, and side effects.

Furthermore, Genomas will be the genomic services provider in applications submitted for SBIR, government and private foundation grants totaling US\$460,000, with additional applications in process totaling US\$525,000.

Mid term

In the mid term, Genomas will provide PhysioTypes as predictors of response to diet, exercise and drugs to physicians, patients, and hospitals through the LPH, beginning in the fourth quarter of 2005.

Furthermore, the company will be initiating contracts to discover PhysioTypes for customers

in the healthcare industry through product development partnerships (managed care, diet/exercise, and pharmaceuticals), beginning in the third quarter of 2005.

Long term

In the long term, Genomas will be licensing revenue from the PhysioType intellectual property drawn from product development partners, diagnostic companies and mass marketing of PhysioTypes, beginning in the fourth quarter of 2006. In addition, massive distribution of PhysioTypes either directly through Genomas or by subcontracting to existing laboratory service companies will be initiated.

The underlying vision of the company

A mature PhysioGenomics platform allows us to partner in areas of interest to commercial partners, such as the strategic alliance with Illumina to identify proprietary sets of biomarkers and commercialized gene marker panels for metabolic syndrome. The placement of an early revenue stream through the LPH and ongoing business development in technology partnerships sets the stage for a balanced revenue portfolio. The eventual success of the company will be driven by the wider distribution, mass marketing and sale of PhysioTypes through the diagnostic, pharmaceutical or clinical services industries. The establishment of PhysioTypes as next generation, premium-priced, patent-protected diagnostic systems enabling personalized health is the underlying vision of the company.

Bibliography

1. Ford ES, Giles WH, Dietz WH: Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA* 287, 356-359 (2002).

2. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Executive summary. US Department of Health and Human Services, Public Health Service, National Institutes of

Health, National Heart, Lung and Blood Institute. *JAMA* 285(19), 2486-2497 (2001).

Website

101. <http://www.genomas.net>
The Genomas homepage.