Genomic-Based Cardiovascular Polypill
OneFul Health, Inc.
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Background

We are living in the fourth industrial revolution with automated decentralized production and big data, 3D printing, cloud computing, artificial intelligence machine learning, internet-of-things (IoT), advanced robotics genome exploration, health and medical wearables, augmented reality, and blockchain technology. All these strategies are being used in healthcare to improve lives and save lives by increasing efficiency and accuracy in the healthcare system; and increasing medication adherence, efficacy, and decreasing adverse reactions for patients. People are in charge of their health and disease. This is the time for personalized medicine. People want to learn about their disease, understand the diagnostic process, know the treatment options, monitor the progress, and create an environment to heal (1).

Cardiovascular disease is the major cause of death and disability worldwide. Despite effective medications, adherence is suboptimal in both primary and secondary prevention. The polypill has been developed as a strategy for primary prevention among individuals at high risk and secondary prevention among patients with established cardiovascular disease. Polypills have been approved in more than 30 countries. They are effective in preventing cardiovascular events, increasing mediation adherence, and lowering adverse reactions (2).

Definition

The current polypills available internationally are fixed dose combinations of medications. For cardiovascular disease, the polypill may contain one or more anti-hypertensive drugs, calcium-channel blockers, statins, and an antithrombotic drug. The anti-hypertensive drugs may include angiotensin-converting enzyme ACE inhibitors such as lisinopril, angiotensin II receptor blockers such as losartan, a beta-blocker, or a diuretic such as hydrochlorothiazide. The statin may be atorvastatin, and aspirin is often the antithrombotic drug.

Historic Perspective

The combination of cardiovascular preventive medications into one pill was initially proposed by Professor Sir Nicholas Wald and Malcolm Law in April 2000. They

described a strategy to prevent cardiovascular disease based on a polypill that contained six medications chosen to lower cardiovascular risk factors, which included excessive low-density lipoprotein cholesterol, high blood pressure, and clumping platelets (3). The polypill was recognized by WHO in 2001, and WHO reported three advantages: overcoming poor treatment adherence by eliminating multiple single pills; overcoming inadequate dose by the physician prescribing practices; and improving the cost and availability of the medications (4).

Polypills have minimized toxicity; and allowed decentralization of treatment and task-sharing by simplifying prescribing and monitoring requirements. This has improved medication adherence, and patient and provider preference over multi-pill regimens. WHO noted operational benefits of the polypill by increased security of supply systems and lower drug supply costs associated with improved production, storage, transport, dispensing, and other health system components.

Specific Studies

Randomized, placebo-controlled trials have confirmed that the polypills improve blood pressure and cholesterol compared to usual care. Munoz et al. used a polypill containing atorvastatin,10 mg; amlodipine, 2.5 mg; losartan, 25 mg; and hydrochloro-thiazide, 12.5 mg. The monthly cost of the polypill was $26, and the adherence at one year was 86%, and there was a significant decrease in systolic blood pressure and low-density lipoprotein cholesterol compared to the usual care group (5). Two studies in the UK showed healthcare system cost-reduction results (6,7). Yusuf et al. showed that a polypill plus aspirin led to a significantly lower incidence of cardiovascular events than did placebo (8). Sukonthasarn et al. discussed the concept that polypills would favor unhealthy habits by the belief of living in a drug-protected state, and a data meta-analysis showed polypill-based care did not lead to neglect of lifestyle risk factors (9). These investigators further showed the need for a genetic-based polypill. Polypill studies in Mexico showed decreased inflammatory lipoprotein levels (10), and in Spain showed decreased systolic blood pressure preventing cerebrovascular disease (11).

Pharmacogenomics (PGx)

A person's genetics and response to a drug is referred to as pharmacogenomics, which now forms the basis of personalized medicine (12-13). Drug metabolism is extremely complex involving multiple enzymes, dysfunctional genes, adverse interaction among drugs, and interference with certain types of foods. A person's DNA analysis and predictive response to specific drugs, known as PGx data, are now readily available at a

low cost, and will help determine likely effectiveness and safety of every medication prescribed. OneFul Health, Inc. and several other companies have demonstrated how PGx data can be used to improve prescriptions using a patient's genomic factors to predictively select optimal drug and dosing for individual patients.

There are more than 50 cytochrome P450 (CYP450) enzymes in the liver and elsewhere that are utilized for drug metabolism. Each specific gene determines one of these enzymes. Every person inherits one gene from each parent, and two healthy genes are needed for effective and safe drug metabolism. DNA analysis detects lacking or abnormal genes. Persons with two dysfunctional genes are considered slow metabolizers or slow responders, and those that inherit multiple dysfunctional gene components have excess enzyme activity and referred to as rapid metabolizers. Drug response can also be caused by genetic variations in drug transporters and drug receptors.

Some drugs are CYP450 inhibitors decreasing drug activity, and others are inducers, increasing activity. It's important to test the DNA before a person takes a medication to eliminate life-threatening adverse reactions. For example, slow metabolizers result in drug accumulation in the body causing toxicity. This is not a minor occurrence, about one-half the population in the United States have a low amount of a transferase enzyme in the liver that metabolizes certain drugs slowly, and the drug can reach higher blood levels and remain in the body longer. Others metabolize drugs so fast that their blood levels never become high enough for the drug to be effective. Another example is that up to seven percent of people are slow metabolizers for a beta-blocker medication used for treating high blood pressure, and this may be used in the polypill. Some types of calcium channel blocker can act as an enzyme inhibitor causing toxic levels of other cardiovascular drugs. This issue can even occur with anesthesia agents where a genetic dysfunction causes a life-threatening disorder called malignant hyperthermia.

This means that a person should have their DNA profile available before taking a medication, which will eliminate serious adverse reactions and eliminate ineffective medications. In the past, DNA testing has been too complex and too expensive for general use; however, OneFul Health has developed a fast, inexpensive method for using DNA testing for safe and effective medications as a clinical aid to physicians in creating personalized prescriptions using genomic data.

Regulatory Perspective

Each one of the medications included in the polypill have been approved by the FDA and used for many years. These medications are generic medications that are less expensive and not requiring FDA approval. Multiple clinical trials including those specifically of polypills have shown that these drugs can be taken together with no drug to drug or metabolic implications, showing safety and efficacy when used.

OneFul Health, Inc.

There have been several issues limiting polypill use; however, OneFul Health has addressed each one of them.

Titrating doses has been an issue because clinicians are trained to change dose according to each patient's response, and the fixed dose of a polypill will not allow for such change. OneFul Health has overcome this by using its patented robotic automation to accurately titrate each drug in each patient's formulation to match a physician's prescription. By providing clinical decision aids that use the patient's DNA to determine the best dose, this polypill formulation should further improve the efficacy of the personalized polypill. Every polypill can be based on the unique person's metabolism in accordance with PGx data and patient's DNA analysis through this online physician tool.

Another concern is that an adverse reaction from one of the medications results in discontinuation of all of them. OneFul Health can improve this by using the patient's DNA analysis to eliminate any medication that will cause an adverse reaction or to recommend an alternative medication when the standard protocol calls for a drug to which the patient is likely to be non-responsive.

Patients may have difficulty swallowing medications in a pill or capsule form. OneFul Health has the ability to make suspension-based delivery to ease swallowing that will improve adherence for pill-averse patients.

A final problem for all individuals taking an anti-hypertension medication is falling from a sudden loss of blood pressure. OneFul Health has proposed a wearable device signaling low blood pressure preventing unexpected falls.

Summary

OneFul Health has the capabilities to revolutionize the polypill concept by accurately combining a physician's multiple drug recommendation for an individual patient into a

single digital prescription using its technology platform. The combination of multiple drugs into a single delivery form has been proven to make a significant improvement in adherence. Using the patient's DNA profile for the type and dose of medication in the polypill for the right drugs at the right doses minimizes adverse drug reactions. This improves disease management and an improved quality of life. This personalized polypill concept can be applied in a broader sense for all medications by using the DNA profile to determine the type and dose of a medication before filling the prescription which will improve lives and save lives worldwide.

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