Abstract:

A Breakthrough Test to determine whether a patient with diabetes is at increased risk of death from cardiovascular disease and developing renal failure and how to prevent these complications

Diabetes Mellitus (DM) currently afflicts nearly 300 million individuals worldwide and the risk of an individual born today is one in three of developing diabetes. DM results in a dramatic reduction in the duration and quality of life due to the development of vascular complications developing 10-15 years after its onset affecting the heart, kidney and eyes. Over 75% of all individuals with DM die due to heart attacks directly as a result of DM. In addition about one-third of all DM individuals lose their kidney function and require expensive and burdensome dialysis treatment and over 10% of DM individuals lose part or all of their vision. The public health cost of DM is also staggering-principally due to management of the complications. World-wide costs of treating DM and its complications exceeds $500 billion per year. Finally, there is a tremendous disparity world-wide and by socioeconomic class in the treatment that is affordable to the individual with DM. Many of the medications currently considered to be standard of care to prevent DM induced complications are too expensive for individuals of lower socioeconomic class or in the developing world. In this presentation we will present a personalized treatment approach to the management of DM based on the identification of a genetic polymorphism that predicts which individuals with DM are at greatest risk of complications and which individuals will receive benefit from a very cheap treatment ($10/year) that can reduce the incidence of heart attack, stroke and death by over 50%. This pharmacogenomic approach to **disease prevention** for individuals with DM represents the first application of personalized medicine to a major disease.

Their exists two common alleles at the haptoglobin (Hp) locus at chromosomal coordinates 16q22 denoted allele 1 and allele 2. A given individual's Hp genotype can therefore be described as being Hp 1-1, Hp 2-1 or Hp 2-2. The prevalence of the three Hp types worldwide is approximately Hp 1-1 (15%), Hp 2-1 (50%) and Hp 2-2 (35%) making this a very common polymorphism. We have demonstrated in multiple independent longitudinal studies that individuals with the Hp 2-2 genotype and DM have an approximately 3-5 fold increased risk of developing cardiovascular disease (heart attack, stroke and cardiovascular death). This association between the Hp genotype and DM complications has been strengthened by transgenic mice and mechanistic studies.

Based on published mechanistic studies we proposed that antioxidant therapy may be beneficial to Hp 2-2 DM individuals. Over the past 10-15 years multiple antioxidant studies done in man have been failures-not only failing to demonstrate benefit but actually showing net harm (over increase in mortality of 5%) from indiscriminate antioxidant therapy (principally with vitamin E). We proposed that this failure was due a lack of proper patient selection. We hypothesized that Hp 2-2 DM individuals would receive benefit from antioxidants. We first tested this hypothesis by retrospectively analyzing stored blood samples from the HOPE study and found that whereas no benefit was found from vitamin E in HOPE overall in the Hp 2-2 DM cohort CVD death and MI were reduced by over 50%. We then went on to prospectively test this hypothesis in collaboration with Clalit Health Services in a prospective double blind placebo controlled study in 47 primary health care clinics in Northern Israel and demonstrated that vitamin E reduced the incidence of MI and stroke and CV death by over 50%- recapitulating the results of HOPE.

We have developed a high throughput method for Haptoglobin typing which is **easily** and **rapidly** performed from 20 µl of serum or plasma using Biorap's **ELISA based assay**. The test is performed **once in a lifetime**. The **high accuracy** (99%) of this ELISA test in determining the Hp genotype has been validated **in over 8000 individuals with Diabetes from eight different clinical studies**. The Hp test will indicate to the physician and the patient to which of the three Hp types the patient belongs (Hp 1-1, Hp 2-1 or Hp 2-2) and on the basis of this information the risk of developing cardiovascular and renal diseases and the prevention opportunities.

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