Saving healthcare costs by implementing new genetic risk tests for early detection of cancer and prevention of cardiovascular diseases

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I. Early cancer detection saves money and lives - resources need to be shifted from expensive treatments to smarter screening strategies

II. Targeting more aggressive prevention therapy for patients at higher genetic risk for heart attack and stroke

The US taxpayer funded the bulk of the human genome project creating the draft sequence of 3 billion letters of our genome. Congress also supported the HapMap project which catalogued the bulk of common genetic variation across several populations. Combining this knowledge with more cost-effective ways of measuring DNA variation in very large patient collections in Iceland, US, and Europe, we have discovered and validated the strongest genetic risk markers for prostate cancer, breast cancer, heart attack, and stroke. These markers are not determinative as are the genes associated with rare genetic diseases like Huntington’s disease; rather, they are used to define patients who are at higher risk than the general population. Genetic risk tests using these markers are clinically available now and may be implemented into best patient care practices to target patients at highest risk for these common diseases for prevention and early detection. This may lead to more cost-effective allocation of established diagnostic and prevention strategies to higher risk patients, resulting in saving of money and lives.

The costs of genetic testing have also greatly decreased, especially when testing for 25 of the most common diseases in parallel. DNA fingerprinting using a million markers allows for future updates without incurring additional testing charges.

While some advocate waiting until we have shown through large randomized clinical trials that these markers ultimately change outcomes over a 10 year period, such trials would cost billions of dollars and ultimately delay the benefits that come from measuring and targeting risk today. In contrast to new drugs with unknown safety profiles which do indeed require clinical trials to determine risk and benefit, the benefit of defining and targeting risk with diagnostic tools has been well validated for these common diseases- the genetic risk tests only provide a more complete targeting of higher risk patients when added to traditional factors. Therefore, they serve to complement and enhance the established best patient care practices of today. The approach that emphasizes early detection and prevention will transform the healthcare from a reactive system to a proactive preventive system with more efficient use of resources.
I. Early cancer detection saves money and lives - resources need to be shifted from expensive treatments to smarter screening strategies

Avastin is thought by many providers to be a wonder drug for late-stage breast cancer. It chokes off the blood supply to tumors and can save the lives of women with late stage cancer. However, it is an expensive drug to manufacture and costs up to 100,000 dollars for just the drug - accessory costs and palliative care for those who do not respond pile on to explode the price tag. Clearly our healthcare system cannot sustain such great but expensive technology. For every woman, driven by her genes and environment to develop breast cancer, whose cancer is diagnosed early instead of late, the health care system saves hundreds of thousands of dollars. Like breast cancer, the most common cancer in women, prostate cancer is the most common cancer in men. Both cancers are the second leading cause of death for their respective sexes and major sinkholes of medical costs. These two cancers cannot be blamed on lifestyle ills like smoking – so that claiming we can solve this problem just by convincing citizens to lead a healthy life is not the answer.

To save our healthcare system from fudiciary collapse, we need to move as many women and men from the late cancer category to the early category. How do we do that? Only five percent of the health care dollar is used to diagnose diseases while 95 percent is devoted to treatment of disease after it is diagnosed, early or late. If we can somehow allocate a little more of the budget to early detection and prevention in patients diagnosed as high risk, we could substantially decrease the huge treatment side of the healthcare budget. However, until now, we did not have the diagnostic risk tools to measure intrinsic risk for future common diseases. The explosion in genetic studies of common diseases such as breast and prostate cancers after the sequencing of the human genome has led to the discovery of widely replicated genetic variants that we are born with that confer risk to common diseases- that is, we have found a small number of key differences in 3 billion letter genetic code that are more common in patients with a disease than in normal individuals and can be used to determine who is most at risk. These markers are also independent of whether the patient has a family history of cancer and so can be useful to define genetic risk in individuals without known family history of these cancers, which includes 85 to 95% of us.

Genetic screening for prostate cancer can identify the 15% of the population accounting for 30% of cases.

For example, the only conventional risk factor for prostate cancer in white males is family history of early prostate cancer in the father or brother- this doubles the risk for prostate cancer from 16 percent to 32 percent lifetime risk. Fewer than 5 percent of males have this risk factor- therefore, 95 percent of white males are considered average risk and are told to wait until age 50 to begin screening for prostate cancer by a yearly rectal examination to feel for hard nodules of cancer in prostate and yearly blood test
measurement of prostate specific antigen (PSA). The higher risk patients are encouraged to begin screening by age 40 or 45.

Through our large genetic studies using over 10,000 patients and 30,000 controls in Iceland, US, and Europe we recently found 8 genetic differences which together define 10 percent of the male population with two-fold risk for future prostate cancer. This is the same level of risk contributed by a family history of early prostate cancer. These markers have been confirmed by our laboratory and others in tens of thousands of patients and controls and published in the leading scientific journals. About one percent of the male population has a 3 fold risk or almost 50 percent chance of developing prostate cancer in their lifetime. These genetic risks are independent of family history—so about 15 percent of white males either have a family history of early prostate cancer or are higher risk based on our genetic test—these 15% of men account for 30 percent of all prostate cancer. Some of these markers also further increase risk for African-American males who already have a higher baseline risk for prostate cancer than white males. Just imagine if we can direct extra resources to identifying these higher risk patients and then follow them closely and earlier using the existing diagnostic methods including yearly examination and blood sampling for PSA, and then ultrasound with biopsy as indicated. Higher risk patients who have a more subtle rise in PSA may benefit from earlier biopsy as recommended by some professional societies. Early detection of prostate cancer when the tumor is still restricted to the walnut size prostate gland usually results in a cure by surgery or local radiation. In fact, no one should die of prostate cancer and the healthcare system should not be saddled with the costly treatments of late stage cancer, if most patients can be targeted for earlier diagnosis.

Targeting women at higher genetic risk for the common forms of breast cancer even if they do not have a family history

Breast cancer may also benefit from focusing on higher risk women even if they do not have a family history of breast cancer. Our validated test of 7 genetic markers can define the 5 percent of women who have about 2 fold risk and about 1 percent with 3 fold risk of the common forms of breast cancer. This test does not predict risk for women who have the rare form of breast cancer with a strong family history of early cancer, covered already by BRCA1 and BRCA2 testing. Instead the test covers risk for the common forms of breast cancer which account for 95 percent of breast cancer. The test defines another 5 to 15 percent of women who may be higher risk despite the lack of family history and who therefore may benefit from earlier mammography or breast MRI, which is more successful than mammography alone in picking up early breast cancer. Higher risk women may also benefit the most from chemoprevention with tamoxifen and raloxifene.

My own case study of how measuring my genetic risk for prostate cancer led to successful early detection and treatment of high grade cancer.

I have already benefited from these new genetic risk tests for common diseases. Last spring I received the results of deCODEme, our comprehensive genetic test which measures 1 million markers and annotates the genetic risk of 25 common diseases; it also
includes our prostate cancer test. I found through my online genetic profile that my risk for prostate cancer was about twice that of the general population. As I was 48 years old at the time, the best patient care practice guidelines recommended that I wait until my fifties to be screened for prostate cancer by rectal examination and the blood test, PSA. However, given my higher risk, my primary care physician ordered a PSA, which came back in the high normal range as 2.0 (conventional normal range is 0.0 to 4.0 but some have lowered the bar to improve the sensitivity of the test). Because the PSA test is not highly accurate, patients will normally have repeat measurements of PSA over an 18 to 24 month period to see if the PSA is rising, indicating that a tumor is growing. However, I was referred to a urologist who agreed that I should be more aggressively screened for cancer than other men with average risk. The urologist biopsied my prostate and found high grade cancer on both sides of my prostate which was surgically removed for presumed cure. Had I waited a few years before getting screened for prostate cancer, there was a good chance that the tumor would have spread beyond the prostate. As there is no useful chemotherapy for prostate cancer, spread beyond the gland often leads to a long painful and expensive course and eventual death. I think it is likely that the genes that we discovered and developed into a genetic risk test saved my life and will be useful to prioritize resources to early detection in other higher risk patients.

II. Targeting more aggressive prevention therapy for patients at higher genetic risk for heart attack and stroke

A common genetic risk factor for heart attack can target some patients who have higher risk than thought based on conventional risk factors

Cardiovascular disease is still the number one killer and health care expense despite the demonstrated benefit of LDL-cholesterol reduction by statin therapy. The number of heart attacks and death rate from heart attacks have decreased over the last decade showing the benefit of screening for higher risk patients using traditional risk factors like blood pressure, cholesterol, diabetes, and smoking, and treating each risk factor. Best patient care practice guidelines also recommend compensating for overall risk by further reducing LDL-cholesterol levels below normal in higher risk patients. However, we do not yet know all risk factors for cardiovascular disease and further improvement can be made by more accurately measuring cardiovascular risk once we do. We and others discovered a new major risk factor for heart attacks that is based on a common genetic factor that 20% of the general population has. This genetic marker has been replicated in tens of thousands of patients and controls in the US, Europe, and Asia and is very easy to measure in a blood sample or inner cheek swab. It is clinically available from our regulated reference laboratory. It is as important as LDL-cholesterol in terms of its magnitude of risk. Prospective studies have shown that the genetic marker significantly improves the accuracy of MI prediction – it reclassifies some who are thought to be of average risk into a higher risk category. Best patient care practice guidelines would suggest that those patients would benefit from a lower LDL cholesterol target level to compensate for their higher risk.
The strongest genetic risk factor for stroke can help diagnose and treat a hundred thousand patients, annually, who have undiagnosed atrial fibrillation as their cause for stroke.

Despite the successes in reducing the number of heart attacks using risk measurement and targeted statin therapy, the annual rate of stroke continues to rise—this year there will be an estimated 800,000 strokes and 300,000 ministrokes (TIAs) in the US. Soon stroke will surpass heart attacks as the most frequent cardiovascular event. Much of the increased stroke rate is due to the aging of the population stemming in part from reduction of death rates due to heart attacks. However, statins are not as effective in prevention of stroke as they are for heart attacks, probably because the causes of stroke are not all tied to atherosclerosis (hardening of the arteries).

We discovered and validated genetic markers that double a patient’s risk for atrial fibrillation, a common cause of heart rhythm disturbance. Atrial fibrillation (AF) is known to cause about 15% of strokes (causing a blood clot to form in the heart and to move to the blood vessels to the brain). However, we have shown and confirmed in numerous populations that the genetic markers for AF are the strongest genetic risk factors for stroke in general. Our work showed that AF is a much more common cause of stroke than originally thought. As many as a third of patients diagnosed with carotid stroke or with stroke of unknown cause, instead have AF that is not originally detected while they were hospitalized for their stroke. We estimate that at least 100,000 patients each year are misdiagnosed as having carotid stroke or stroke on unknown cause instead of having AF as their cause for stroke. This means that AF strokes are twice as frequent as currently thought. This is a large problem because prevention of AF stroke is different than prevention of other types of strokes. Anti-platelet drugs like aspirin and Plavix reduce carotid and small vessel stroke risk, but they have little or no effect on AF-related strokes. Instead, warfarin is the drug of choice for AF strokes and reduces stroke rate by 60 to 70%. AF-related strokes are the worst strokes to have since they cause greater disability and higher death rates than other types of strokes. The recurrence rate of AF related stroke is higher as well—12 to 19 percent of AF stroke patients will have another stroke within the first year.

Defining patients at highest risk for AF using genetic markers and other risk factors may lead to more targeted outpatient cardiac monitoring, resulting to better primary and secondary prevention of AF strokes. Because each stroke prevented saves the health care system an average of 65,000 dollars over 4 years, the ramifications of targeted prevention are immense in terms of saving of costs and lives. For example, successful prevention of just half of the 100,000 AF strokes per year could save CMS billions of dollars. Because African-Americans have a higher risk for stroke than whites, this approach may have an even greater benefit to address this healthcare disparity.