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Genomic Epidemiology of Diabetes Type 2, Pharmacogenomics and the Relevant Health Education Implications in the Age of Genomic Medicine

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ABTRACT

This project investigated genomic epidemiology of diabetes type 2; the clinical and non-invasive methods for diagnosis were succinctly summarized. The modifiable and non-modifiable risk factors associated with the disease were analyzed. As one of the leading causes of mortality and morbidity in United States, the economic burden associated with this disease was assessed. Trends in the morbidity and mortality of diabetes type 2 revealed an increase in the disease frequency into the twenty-first century. While the modifiable risk factors were discussed with suitable interventions, the non-modifiable risk factors demand prompt medical diagnosis and treatment. The genes incriminated for diabetes type 2 were listed. The relevance of pharmacogenomics cannot be overstated in pre-empting and weakening most of the indicted genes, before their disastrous impact becomes uncontrollable at the primary and secondary stages of their morbidity. This innovative intervention derived from pharmacogenomics has not been comprehensively integrated into either clinical medicine or in health education of the at risk population. By far most important, is the consumption of food items rich in phytochemical-nutrients to maximize public health and minimize the impact of diabetes not only in United States but also worldwide.

KEY WORDS: Genomic epidemiology, indicted genes for diabetes type 2, Public health genomics, modifiable and non-modifiable risk factors, national economic burden from diabetes, invasive and non-invasive interventions, pharmaco-genomics, and phytochemical-nutrients

INTRODUCTION

Mausner and Bahn[1] defined epidemiology as "the scientific study of the determinants and distribution of diseases and injuries in human population." In the same vein, genetic epidemiology has been conceptualized as the science which focuses on assessing the etiology, distribution and control of disease in groups of people with intra-familial linkage with inherited causes of disease in population. Khoury and Associate[2] further explained genetic epidemiology as "the study of the role of genetic factors and the interaction with environmental factors in the occurrence of diseases in populations." Genomics implies the interaction of genes with other genes and the environment. Genome-based innovative technologies have revolutionized scientific knowledge about the incipient onset of diabetes, and the most efficient mechanism of managing this disease so as to minimize the lethal consequences of this chronic disease.

From clinical epidemiologic studies, diabetes type 2 is a condition characterized by high blood glucose levels caused by either a lack of insulin or the body's inability to use insulin efficiently. Type 2 diabetes develops most often in middle-aged and older adults but can appear in young at risk persons, mostly if there is intra-familial linkages with parents who suffers from diabetes. **Type 2 diabetes** is a chronic disease characterized by high levels of sugar in the blood and the disease develops when one's body does not respond correctly to insulin (a hormone released by the pancreas). The most common form of diabetes is type 2 diabetes. The major precursors for diabetes type 2 are being overweight, especially in the abdominal areas, increases one's chances of developing type 2 diabetes. Other factors, such as family history, sedentary lifestyle and diet excessively rich in lipids, high in sodium and sugar, can significantly increase one's risk. Type 2 diabetes usually develops gradually and may not have any noticeable symptoms. The presence, severity and number of symptoms vary from person to person. Symptoms that may be experienced include, but are not limited to: blurred vision fatigues low-healing infections increased thirst and a high frequency of micturation.[3]

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Clinical Diagnosis

Epidemiological studies have revealed that type 2 diabetes is a complex metabolic disorder involving abnormal hepatic glucose output, insulin resistance, and dysfunctional insulin production. Based on CDC[4] clinical guidelines, diabetes type 2, specifically accounts for 90% to 95% of all diagnosed cases of diabetes. Degrading type 2 diabetes, the pancreases continues to secret insulin but the body is unable to use the insulin efficiently; this discomfort is characterized as insulin resistance. Eventually, as the need for insulin increases, the pancreases gradually lose its ability to produce insulin.

The major precursors associated with type diabetes are family history, old age, history of gestational diabetes, impaired glucose metabolism, excessive consumption of salt, impaired glucose metabolism and sedentary lifestyle.[4] Based on the Federal Centers For Diseases Control and Prevention[4] epidemiological analysis, the incipient stages of diabetes type 2 develops slowly over the years, when screening could reveal specific genes chromosomes associated the disease. In fact, well developed knowledge about pharmacogenomics is now recognized to eliminate or significantly reduce the risks associated with the disease thereby eliminating the social problems of loss productivity, amputation of patients' legs, and the unnecessary mortality and morbidity attributed to diabetes.

Currently, the medical complications suffered by those suffering from diabetes consist of kidney dysfunction, neurological disease, retinopathy, stroke, leg ulcers, amputation and needless death.[4]

Physicians and other clinicians are able to identify the early onset of diabetes by obtaining the fasting blood glucose screening and performing clinical analysis to detect quantitative values that are indicative of pre-diabetes and diabetes type 2. As illustrated in Table 1, patients suffering pre-diabetes have elevated blood glucose, however, it not high enough to be classified as full-fledge diabetes type 2. Individuals with pre-diabetes are at a high risk of developing diabetes type 2 mostly if they neglect their risk factors. It is at the incipient stage of this disease that pre-emptive interventions can be applied to suppress or eliminated the adverse effects of indicted genes chromosomes

Table 1
Diagnosing Diabetes and Pre- Diabetes

	Fasting Blood Sugar	**Random Blood Sugar**	**A1C Blood Test Result**
Normal	**< 100**	**< 140**	**< 5.7 %**
Pre- Diabetes	**100 – 125**	**140 - 200**	**5.7% - 6.4%**
Diabetes	**≥126**	**≥200**	**≥ 6.65%**

In an effort to avoid leg amputation and the other morbidity and unnecessary death associated with diabetes type 2, this project was designed to:

Explore the national economic burden associated with diabetes

Explore the morbidity and mortality associated with diabetes type 2

Explore genomic epidemiology of diabetes type 2

Identify modifiable and non-modifiable risk factors associated with diabetes type 2

Propose nutritional interventions to combat diabetes type 2 and

Advocate the adoption of predictive, preventive, personalized and participatory approaches to reduce the mortality and morbidity associated with type2.

Economic burden associated with diabetes

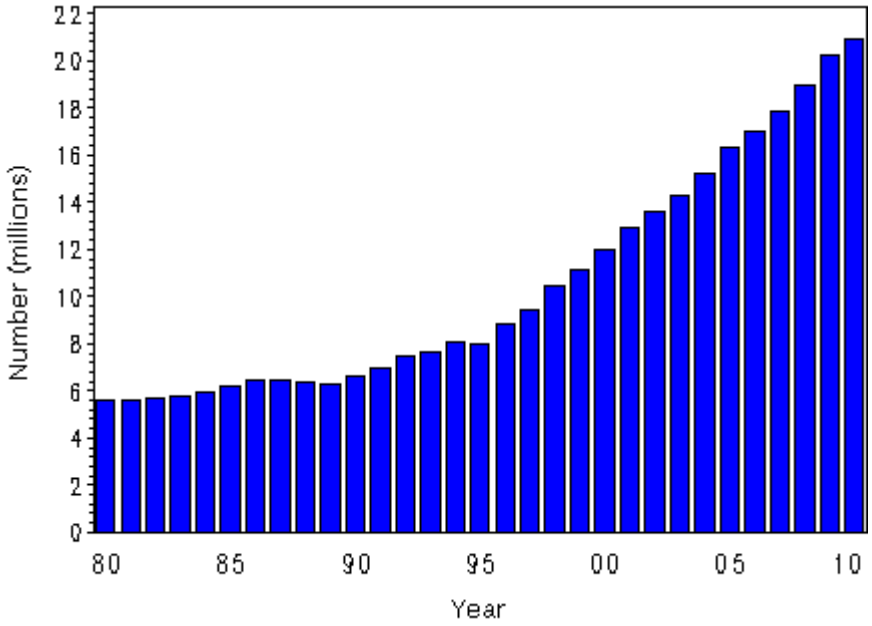
Just as the morbidity and mortality attributed to diabetes increases into the twenty-first century, the financial burden incurred from the cost of managing full-blown diabetes continues to increase exponentially. By 2007, the estimated costs of diabetes amounted to S174billion, including $116billion in medical expenditure, and over $58billion in lost productivity. In the same year, $27billion was expended to treat diabetic patients directly, and $58 billion was spent treating patients of diabetes-related medical complications.[4] For patients with diabetes, the indirect cost from absenteeism was estimated to be $2.6billion and reduced productivity was $20billion for those employed and reduced productivity was $0.8billion for self-employed workers. CDC also estimated the financial resources lost to diabetes from those unemployed due to diabetes-related disability at $7.9billion. The cost associated with lost productivity resulting from untimely death as $26.9billion.[4]

Trends in Morbidity and Mortality Associated with diabetes type 2

The prevalence of diabetes in the United States continues to rise basically from excessive sedentary lifestyle, dietary intake, and family history. Between 1980 and 2010, the frequency of Americans diagnosed with diabetes has

more than tripled. The upsurge observed from CDC's data revealed 5.6 million in 1980 to 20.9million in 2010. Within the two decade, the crude prevalence of diagnosed diabetes patients increased by 176%(from 2.5% to 6.9%).[4]

Figure 1
Number (in Millions) of Civilian, Non-institutionalized Persons with Diagnosed Diabetes, United States, 1980–2010



Source: CDC, 2012

Diabetes is becoming more common in the United States. From 1980 through 2010, the number of Americans with diagnosed diabetes has more than tripled (from 5.6 million to 20.9 million).

Within the same period, the crude age adjusted prevalence of diagnosed diabetes were not only similar but provided a strong indication that most of the increases were not merely due to the aging population but created by nutritional, and social-behavioral anomalies.In assessing the ethnic differences regarding prevalence of diabetes, between 2007-2009, 7.1% were non-Hispanic whites, 8.4% Asian Americans, 12.6% non-Hispanic blacks and 11.8 Hispanic.[5]

Modifiable and Non modifiable Risk Factors

Several years of basic medical and behavioral research studies sufficiently identified the modifiable and non-modifiable risks factors associated with diabetes. Albeit, the cure for diabetes was not confirmed, diabetes was therefore characterized as a chronic and degenerative disease. Clinicians and health educators are aware that compliance with the prompt primary preventive activities can mitigate the occurrence of leg amputation, neurological diseases, blindness and unnecessary death; the modifiable risk factors were used by behavioral scientists and nutritionist to educate and create self-management strategies for most patients. Those with diabetes were provided health education about avoidance of sedentary lifestyle, avoidance of food items rich in lipids, obesity, and avoidance of stressful lifestyle and having adequate amount of sleep on a regular basis. The non-modifiable risk factors consist of family history, the aging phenomenon, mostly being in the cohort of 60 and over, previous gestational diabetes and ethnicity.

Accomplishment of the Human Genome Sequencing (HGS)

After the successful completion of the human genome sequencing project by March 2003, the International Human Genome Sequencing Consortium (IHGSC), and many other organizations publicized the impact of this global scientific breakthrough. In fact, genomics has created the momentum which could revolutionize the twenty-first century as the era of biological pre-eminence.[6] The predictions are that everyone will be affected by the spin-off benefits of technologies associated with genomics. Besides, when on-going research and biotechnology developments are fully implemented, the current medical practice will become obsolete. Understanding of human

genetics and genomic profile will create the foundation for intense research in innovative medicine, agriculture and the various biologic sub-disciplines which could illuminate the inner workings of the entire biological systems. Patrinos[7] admits that "sequencing the human genome was a pioneering venture with risks and uncertainties. But its success has created a revolution-transforming biological science far beyond what we could imagine. We have the door into a vast and complex new biological landscape. Exploring it will require more creative thinking and new generations of technologies." Walport[8] of the Wellcome Trust remarked that the enormity of the Human Genome Project is unprecedented in biology and he praised the international vision and collaborative efforts of the scientists who were involved in this global scientific breakthrough.

The practical value-added impact of genomics are being realized by the industrialized nations in innovative medical scientific breakthrough, agriculture, forensics, identification science, microbial ecology, toxic waste management, and the mysteries of evolution, anthropology, sociology, and human migration patterns. The prediction by the international scientific community is that genomics and biotechnology will have profound impact on engineering, computer science, mathematics, ethics, religion, law, agriculture education, pharmaceuticals, instrumentation, nuclear medicine, forensic science, bioremediation, bio-fuels, and journalism.

As the enthusiasm about genomics surged, the promise of this unprecedented scientific feat was that everyone regardless of race, citizenship, national origin would reap the benefits of genomics and the multifarious applications. There would be increased life expectancy, low infant mortality rate, remunerative career prospects for young graduates and improved health status for newborns and their mothers. The trepidations in the developing nations are many and varied: they have echoed lack of scientific infrastructures to harness the benefits of research derived from genomics, they also confront the challenges of insufficient financial capital to establish viable comprehensive genomic sequencing centers and inadequately trained workforce to conduct rigorous and meaningful research in curative and preventive medicine, agriculture, plant genomics, bio-processing and other value added economic outcomes associated with genomics.

Regarding type 2 diabetes, a series of genome-wide association scans for type 2 diabetes are being used to identify genome-related type 2 diabetes gene chromosomes. The sequencing of the human genome has created significant impact in clinical medical practice and health education of the public.

Genomic Epidemiology of Diabetes Type 2.

Genomic epidemiology investigates the determinants and distribution of diabetes in human population. It also investigate the characteristics of the at risk groups, and the genetic risk factors of diabetes and the haplotype features of those with diabetes and the most appropriate interventions to ameliorate the impact of the disease. One of the most significant milestones derived from genomics, is the innovative molecular knowledge derived from this innovative science which enable scientist to identify new disease gene, sequence them and possibly pre-empt their deleterious impact before they unfold in the secondary and tertiary stages of disease (such as diabetes when their prevention becomes ineffective. To illustrate, Dr. Elias Zerhouni[9] former director of the USA, National Institutes of Health (NIH) has on many occasions advocated the impact of genomics in revolutionizing the current practice of medicine and public health science. He has repeatedly drawn the attention of the international scientific community and political administrators to the collaborative research venture between the National institutes of Health and the Finnish research team which identified at least four gene chromosomes associated with diabetes. By 2002, he reported there were only two genes that had been sequenced, but by 2008, there were 7 and today, over ten gene chromosomes were successfully sequenced to be associated with diabetes type 2, a life-threatening disease known to affect over 200million people worldwide[9]

Rich, Norris and Rotter[10] have corroborated the assertion of Zerhouni about diabetes type 2 as one of the most insidious public health problem confronting western civilization. Based on their observations, 4,100 people in United States are being diagnosed daily with diabetes. Among the patients, each day, 230 have their legs amputated, 120 are placed on kidney dialysis and 55 become legally blind. Approximately, 21 million people endure the morbidity associated with diabetes, with one in five patients over the age of 60. Data on the leading causes of death in United State pinpoint diabetes as the sixth leading cause of death. Patients with diabetes face twice the risk of death as individuals of the same cohort without diabetes. To reiterate, the estimated cost of diabetes to the United States economy I nearly $132billion in lost productivity and indirect medical cost.[11]

Sequenced Gene Chromosomes for Diabetes Type 2

With diabetes type 2 recognized as multi-factorial in it transmission, initially, there were only two gene chromosomes associated with the disease.[12] The first of the 10 new gene chromosomes identified **was the common polymorphism of the transcription factor 7-like 2 gene (TCFL 2); and the other variants being the rss12255372 and rs 7903146.** With innovative diagnostic techniques derived from genomic science, the

international HapMapproject enhanced genomic analysis and sequencing of many other gene chromosomes associated with diabetes type 2 based resources from the International HapMap Consortium.[13] Currently, Reagents have been developed to cover the human genome at 5-kilobyte resolution and the clinical spectrum of the individual candidate genes are analyzed to facilitate gene discovery.[10]

To augment exiting gene frequencies, with a series of genome-wide association scans, hundreds of thousands of single-nucleotide polymorphisms (SNPs) across the genome have been assayed. These genomic data were derived principally from northern European ancestry. The newly sequenced genes consist of the following: TCF7L2, SLC30A8, IDE-K1F11-HHEX, CDKAL1, CDKN2A,-HHEX, CDKN2B, IGF 2BP2 and FTO among others.[14] To a large extent, the geographic biomes and haplotype characteristics of an areas influence the gene variants. Geneticists now argue that there could be 38 genetic variants associated with type 2 diabetes which have been confirmed The investigators maintain that increasing the size of the meta-analysis could detect many more variants. The Fusion Team has been able to replicate association between numerous genes with risks associated with type 2 diabetes. Recently, the additional two genes sequenced were RAFGEFT and TP53. The team also recommended further investigation to confirm their scientific findings.[10] The investigators suggested that RAPGEF1 represent a strong candidate gene chromosome for two reasons, the primary reason being its role in insulin signaling, and the clinical pathway of RAPGEF1 in regulation of proglucagon gene expression in intestinal endocrine L-cells which substantiate its effects on risk of type 2 diabetes[15]Zeggini, Scot, Saxena Voight[16] in their meta-analysis have confirmed 18 genes for type 2 diabetes. These discoveries demand the application of pharmacogenomic interventions to create the clinical strategies to pre-empt the activities of these deadly gene chromosomes. Palmer[17] has also observed that in terms of disease etiology, medical scientists and researchers are uncovering a wealth of copious knowledge about the pathoetiology of type 2 diabetes. In addition, majority of genetic loci involved in type 2 diabetes are well-routed in the biology of pancreatic beta cells and only associated with insulin resistance to a minor degree. This is exemplified by the seminal discovery of variants in the SLC30A8gene, which seems to be involved in the uptake of zinc, necessary for the production of insulin.[17]

In genomic community, the prevailing intuition endorsed by the international human genome sequencing consortium (IHGC) is, for those nations, research centers, academic scientific institutions, and administrators who by fiat of culture or political dispensation deliberately ignore or trivialize the medical, engineering, economic and social benefits of genomics do so at their own peril. In the next decade, the cost of developing the scientific workforce, procurement of innovative technology required for establishing state of the art genomic centers will become cost-prohibitive. As we peep into the future of HGS, the Battelle Technology Partnership Practice,[18] has emphasized that:

> The advancement of knowledge and the technologies resulting from
> human genome sequencing have formed the platform for nothing less than a medical revolution. The primary impetus of this revolution in quantitative and personalized medicine may not yet be felt in daily clinical practice but that day is accelerating towards us. One of the key realizations that must be understood regarding the human genome sequencing is that its usefulness is perpetual. While other major big science projects have a life attached to them the human genome sequence will not wear out or become obsolete.
> Rather, the reference human genome is akin to chemistry's periodic table, a perpetually useful platform for understanding and advancing science.

PHARMACOGENOMICS

Researchers define pharmacogenomics as the science that investigates how individuals react to medication. The World Health Organization (WHO)[19] has explained pharmacogenomics as the study of DNA sequencing of variation as it relates to differential drug response in individuals. This entails application of genomic technology to determining an individual's response to specific drugs in order to avoid adverse drug events. The United States Department of Energy therefore emphasized thatpharmacogenomics as "moving away from one size fits all" therapeutics. The cogent rationale pertains to the need for medical scientists and epidemiologists to correlate DNAvariants with individual patient's responses to medical treatment and identify drugs which arecustomized to specific cohorts of patients. Therefore the discipline that blends pharmacologywith genomic capabilities is referred to as "pharmacogenomics."

The advantages of this innovative science are many and varied: It can be used to pre-empt and sequester specific gene-chromosome for deadly diseases, contain cost ofManagement of diabetes, enables physicians to avert deadly clinical errors,and protect patients from unnecessary and untimely death and restore their confidence in

medical practice derived from genomic research. Currently the state of the art knowledge about pharmaco-genomics continues to enhance the treatment of very few patients with diabetes, and other chronic and degenerative diseases. In fact, a molecular geneticist at Stanford University(Michael Snyder) has successfully used his knowledge of the link between his DNA and biochemical fluctuations in body over time to adopt the tenets of pharmacogenomics to pre-empt diabetes-related genes which could have easily predisposed him to the onset of diabetes type 2[20]

INNOVATIVE (P4) MEDICINE: PREDICTIVE, PREVENTIVE, PERSONALIZED AND PARTICIPATORY

Today, an improvement in the technology for biochemical analysis of patients' specimen has enhanced the knowledge about the incipient signs of pre-diabetes, and diabetes type 2. The recently developed technologies most relevant to genomics science include 454 life sequencers, manufactured by Roche Diagnostics (Brandford, CT), chromatography and electrophoresis, gene amplification, capillary analysis,polymerase chain reaction tests, micro array sequencing and iso-electric focusing. These innovative technologies and bio-informatics have the potential to provide relevant insights into the disease manifestation in individual patients and the clinical differences at molecular level. It is such knowledge that will enable physicians to tailor treatment to the precise needs of diabetic patients. After the accomplishment of the human genome sequencing (HGS), personalized medicine could include testing for variations in genes, gene expression, proteins and metabolites. In more sophisticated comprehensive patient's assessment, the results of the patient's HGS will compliment anthropometric data which are likely to correlate with drug response, disease state, and treatment prognosis, including patient's behavioral lifestyle such as exposure to stressful lifestyle, consumption of food items rich in lipids, alcohol and other adverse nutritional habits.
Precision medicine which was described by Dr. Elias Zerhouni,[21] the former director of the National Institutes of Health (NIH), is the innovative medicine which must anticipate and interrupt the disease process, thereby preventing the patient from being overwhelmed by the actual disease burden. This innovative medical paradigm is now characterized as P4 medicine:

(1) Predictive approach is the development of probabilistic health projection for a person based on their DNA, or sequenced chromosome, and protein expression.

(2) Preventive medicine is the creation of interventions or therapeutic that will prevent a disease that an individual is assessed to have a high probability of developing.

Regarding diabetes type 2, counseling of young adults which involves the requisite health behaviors, particularly about the avoidance of tobacco, and the ingestion of food items that are rich in lipids, sugar, and salt, avoidance of sedentary lifestyle or physical inactivates, and stress management techniques can be used to avoid diabetes type 2. Although age is a pathogmonomic risk factor, exercise and compliance with adequate health habits can become protective against many diabetes.

(3) Personalized medicine refers to treating individuals based on their unique human genetic variations. For example, what are their sequenced DNA and haplotype characteristics? Does the patient have inherited chromosomes that place such a patient at risk of diabetes?

(4) Participatory medicine implies a patient's active, informed involvement in their medical choices, treatment, and acting in partnership with their health care providers. A patient must be health-educated enough to inform a physician if the parents died from diabetes? Are there siblings who currently have or died from diabetes?
Many technological sequencing devices relevant to diabetes research have been developed in recent times. Such knowledge will enable the physician to tailor treatment to the precise needs of patients. A comprehensive list of the state of the art technologies required to improve the dissemination of personalized health care services was compiled by Ebomoyi and Srinivasan.[22] In the era of genomic medicine, the key benefits of predictive, preventive, personalized and participatory interventions to the patient include new abilities to:

- Detect disease at an earlier stage, when it is easier and less expensive to treat effectively
- Stratify patients into groups that enable the selections of optimal therapy
- Reduce adverse drug reactions by more effective early assessment of individual drug responses
- Improve the selection of new biochemical targets for drug discovery

NUTRITIONAL INTERVENTIONS/NUTRIGENOMICS

Another crucial intervention against diabetes is efficiently tailored nutritional education for patients emphasizing the role of phyto-chemical nutrients in their diet.
Nutrigenomics is intricately linked to the scientific knowledge about the types and quantity of food consumed and their effect in human genome. Research conducted by Oshifuye[23]

Substantiated the chemo-protective impact of cruciferous vegetables such as broccoli and Brussels sprouts in fortifying human immune system and preventing diabetes. Other food items known to reduce the impact of diabetes, include bitter leaves, egg plants and spinach.

RELEVANT HEALTH EDUCATION

The diet of the diabetic patients must be rich in whole grains, whole-wheat pasta, raisin bran, barley, oatmeal, oat brown muffins, brown rice, or whole-wheat bread. Dietary compliance is extremely essential, followed by medication and exercise.

Many phyto-chemical -nutrients derived from vegetables which are rich in vitamins and beta carotenes consist of: broccoli, spinach, dark green leafy vegetables, peas, artichokes, carrots, tomatoes, Brussels sprouts, and potatoes and yam.[24] The combined nutrients from the food items reported contain multiple vitamins such as E which acts as antioxidants assisting in blood to reduce the amount of oxidized low density lipoproteins that are formed. Beta-carotene is among the other vitamins with antioxidants which in human diet aids in reducing the risk of congestive heart disease. The B vitamins consisting of B6, B12, and folic acid (foliate) play vital role in protecting patients against diabetes.

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