Computers in Biology and Medicine 59 (2015) 211–220

Contents lists available at ScienceDirect

Computers in Biology and Medicine

journal homepage: www.elsevier.com/locate/cbm

An Indian eye to personalized medicine

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ARTICLE INFO

Article history:
Received 30 August 2013
Accepted 3 July 2014

Keywords:
G-Card
Healthcare
Human genome
India
Personalized medicine
Smart card

ABSTRACT

Acknowledging the successful sequencing of the human genome and the valuable insights it has rendered, genetic drafting of non-human organisms can further enhance the understanding of modern biology. The price of sequencing technology has plummeted with time, and there is a noticeable enhancement in its implementation and recurrent usage. Sequenced genome information can be contained in a microarray chip, and then processed by a computer system for inferring analytics and predictions. Specifically, smart cards have been significantly applicable to assimilate and retrieve complex data, with ease and implicit mobility. Herein, we propose "The G-Card", a development with respect to the prevalent smart card, and an extension to the Electronic Health Record (EHR), that will hold the genome sequence of an individual, so that the medical practitioner can better investigate irregularities in a patient's health and hence recommend a precise prognosis.

1. Introduction

Companies from private and cross-service platforms will be transacting in customized medicine and pharmacology. Personalized medicine per-se is an enormous challenge given the scope, complexity and usage-population. Also, named as *precision medicine* by few, personalized medicine is yet to see a long road to acceptance and proliferation [1]. But what is in store for a "developing" country like India. Well, there is already some buzz, but much will be uncovered with time and technology. Gupta et al. [2] have rendered an overview of how slow economy directly correlates to lack of early diagnosis and treatment. In the light of biomarker discovery, not only health know-how, but education, behavioral contexts, social ethics, all have a role to play.

2. Human Genome Project: conception to completion

It would not be all appreciably acknowledged if a remark about the HGP is not made [3]. Way prior to that when Watson and Crick presented their work on DNA structure [4], it marked the "true" beginning of the genomic era. It embarked many concerned scientists and researchers to elaborate more on the underlying aspects of the molecular biology. The completion of the HGP in April 2003 had scattered the questions of annotation and genetic contemplation. The rackety nature of the biological data at the molecular level and its overlapping tendency obstructs their acceptance from practical and commercial standpoint.

The then President of the United States, Bill Clinton and the then Prime Minister of Britain, Tony Blair (via satellite) announced the successful sequencing of the human genome and rightfully called it an edifice that will be extremely seminal towards understanding and building upon a new phase of medicine and hospitality [5].

Few people are aware of the fact that the HGP was commenced by physicists, primarily. The U.S. DOE and NIH collaborated for this grand scientific endeavor [5]. After a workshop in March 1986 in Santa Fe, New Mexico, the DOE's OHER, a realization was made by the research fraternity that "despite significant scientific, technical, and financial challenges, there was sound scientific justification to attempt the project and a reasonable expectation that the required technologies could be developed. Participants also agreed on including an educational and social component that examined the project's promises and limitations and the potential ramifications of making genomic information available [5].

Of course, an initiative of such stature invited international urge. Outside the United States of America, agencies gathered quick solidarity for the project initiation and completion. One of the frontrunners that were involved in bringing together all diverse groups was Wellcome Trust, UK [6]. It provided funding support to the project at a tier only second to the United States. It is also noteworthy that the HGP started-off with no roadmaps

Abbreviations: EMR, Electronic Medical Records; EHR, Electronic Health Records; HGP, Human Genome Project; DOE, Department of Energy; NIH, National Institutes of Health; OHER, Office of Health and Environmental Research; NHGRI, National Human Genome Research Institute; HEP, Human Epigenome Project; HPP, Human Proteome Project; DTC, direct-to-consumer; SNP, Single Nucleotide Polymorphism; WHO, World Health Organization; DOHAD, Developmental Origins of Health and Diseases; HIE, Health Information Exchange

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http://dx.doi.org/10.1016/j.compbiomed.2014.07.001
0010-4825/

and was guided more by a vision; so much characteristic to any great scientific endeavor. Albeit certain pre-defined goals were deterministic [5]:

- Identification of ALL the genes in the human DNA.
- Determination of the sequences of the three billion base pairs that make up the human genome.
- Storage of the resulting data in the public databases.
- Improvement of data-analysis tools.
- Transfer of genomic technologies to the private sector.
- Addressal of ethical, legal, and social issues that might arise from the HGP.

The strategies for generating the human genome sequence, as adopted collaboratively by Celera and HGP, are illustrated in [7]. The gamut of HGP was stranded with the inertia and friction of the participating groups that persuaded their own methodologies for carrying out things effectively. These impediments were cleared by Celera Genomics, headed by J. Craig Venter that emerged as a private partnering company [5]. Its involvement was not welcomed by government bodies that had an idea about Celera getting access to public data, augmented to its private sum. [They] were unsure as to how exactly Celera is going to make use of the genome data, but they anticipated that contrary to the mandate issued by the NHGRI, the genome data would not be freely available to the public [5]. As the project neared completion, private–public entities jostled their way through; but humbly, at the end, the Clinton press conference would grade [it] a "tie".

The Human Genome paved way for several subprojects in its category: HEP [8] and HPP [9,10], which further attempt to decode the riddles of inter- and intra-regulation of genes and molecules broadly, in different biological states.

3. Business aspect

Ever since the HGP gained momentum and acceptance, it has been a "guiding star" to most of the drug design and pharmaceutical oriented companies [11]. Working in close reference and tandem with the genomic data, aids efficient and to-the-point analysis. DTC companies are basking in the glory of genomics revolution, formalizing DNA tests that throw light on genetic traits and putative risks associated with disease induction [12].

The status of results offered by DTC (genomics) companies and their usefulness is arguable [12]. However, in a comparison made between two such companies, viz. 23andMe in Mountain View, California and Navigenics in Foster City, California, wherein the 13 disease sets of 5 patients was considered, the analyses reflect the huge potential that beholds under the aegis of personalized medicine [12]. Owing to the non-invasive methods for obtaining DNA samples from the patient viz. saliva, cheek swab, etc., the "first-time users" are less likely to feel apprehensive and reluctant. Tests can be ordered online and likewise is the display of results. The processing is carried out by distinctly identifying set of biomarkers in the particular patient and comparing them to the publically available ones [12].

Both companies (Navigenics and 23andMe), as per the patient data, assume varied parameters or aspects for predicting the proneness of a genetic disease. This directly implies that certain diseases can have better predictions as opposed to others. In an attempt to establish the results, it was found that for seven maladies, 50% or less of the predictions of two companies agreed across five individuals [12]. It is incumbent upon the companies to represent high risks articulately and also suggest biomarkers as potential drug targets. Even though, each company harnesses the same publically available data for elucidating the set of markers, no two companies end up having the same due to the discrepancies in the selection criteria of the risk calculation based on the genome-wide association [12]. Also, for making strong predictions the markers have to be chosen after thoroughly studying mutations in expression levels and being as "modest" as possible. This can however be a subjective matter. The holy grail of predicting genetic disease after analyzing the whole genome sequence and making comparisons with the publically available data is the veracity of biomarkers [12]. The hindsight that the companies must contemplate upon is the community welfare. They must enter into a contract of mutual understanding and should have common grounds on selecting markers that have a thorough and deep-rooted effect.

The two major polarizers with the defined technologies are the readiness to clinical validity and correlation to a disease state [13]. Most often today, the clinical genetic testing is carried out to elucidate the abnormality in a family, wherein the current and/or upcoming generations might be carriers of an aberration and might end up in an innate malady. This is technically commanded under SNPs testing, as opposed to whole genome sequencing, where comprehensive information can be construed to elicit disease traits and gene-wide associations. This scenario presents exciting opportunities as well as defiance for clinical medicine and its compliance to genetic analysis [13].

In addition, as a part of mandatory disclosure, the patient has to be apprised in all transparency about the various aspects of the sequencing procedure and its probable benefits. The legitimacy and validity have to be acknowledged with the greatest regard [13]. The information deciphered from the subject's genome sequencing will be actually quantifiable after it has been clinically verified. The patients must also be warned that they may be susceptible to many associated risks that correlate to behavioral traits and psychological aspects. Every patient will have to undergo distinct self-contemplation and decision making process, so as to ensure what is best for them and their social associations [13]. It may seem like the patient suffers in a short term but at large, in a longer run, on acknowledging the universality of the genomic insight, he/she will definitely benefit meticulously [13].

It is vital to understand that since genetic anomalies can be transferred from one generation to the next, every patient could face some negative social consequences after having children as carriers of the disorders [13]. When dealing with problem of such vast gamut, it will certainly goad a patient into tremendous inquisitiveness and a spate of eagerness will drive him/her into answering those queries and thence would require an expert voice to helm the correspondence into the right direction with as much subtlety as possible [13] (Fig. 1).

The panel (Kelly E Ormond, Matthew T Wheeler, Louanne Hudgins, Teri E Klein, Atul J Butte, Russ B Altman, Evan A Ashley, Henry T Greely) proposes some practical considerations for the use of whole-genome sequencing data in clinical practice, as follows [13]:

- The broad scope of the results will require that patients receive complex and detailed information before they decide whether to be tested.
- Interpretation of genome sequences should take into account the limits of the sequencing method used.
- Easily accessible and well curated information about the links between genomic sequences and diseases needs to be created, maintained, and frequently updated.
- Physicians and patients will have to cope with enormous uncertainty in some results, particularly around variants of unknown importance, which might require analysis of genetic information from family members.
- Effective ways to convey meaningful information to patients about the many implications of their whole-genome sequences