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Genome sequencing practices and the future of clinical research

Abstract

Genome sequencing is one of the latest technologies to be introduced for use in clinical trials. It is often used in the practice of genomic medicine, with the objective of processing information about genes and markers to treat disease. Specifically, genomic medicine uses DNA and RNA platform sequencing technologies to analyze the human genome to detect diseases caused by gene mutations. In 2003, these genomic sequencing platforms (first- and second-generation sequencing technologies) made it possible to complete the Human Genome Sequencing Project, which identified approximatively 35,000 genes in sequences of more than 3billion human DNA and RNA chemical bases. This paved the way for genomic medical practice, enabling researchers to carry out translational genomic clinical studies that have begun advancing the clinical trial process in multiple ways.

Keywords: genomic medicine, DNA & RNA sequencing, clinical research, clinical trial, gene mutations, first generation sequencing, next generation sequencing, technology, human genome sequencing project, gene-gene interactions, gene-environment interaction, genomic

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Yawo M Akrodou
Department of Health Science, Walden University, USA

Correspondence: Yawo M Akrodou, Department of Health Science, Walden University, USA, Email makrodou@yahoo.com

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Abbreviations: GM, genomic medicine; CVN, copy number variation; NGS, next generation sequencing; NIH, national institutes of health; DNA, deoxyribo nucleic acid; RNA, ribonucleic acid

Introduction

Genomic medicine (GM) is the application into medical practice of information about how genes and their markers react with other genes and environmental factors.[1] In recent years there have been rapid advances in genomic sequencing and the greatest achievement of this innovation was the complete sequencing of the human genome, a project that enabled the description of approximatively 35,000 genes by deciphering more than 3billion chemical base pairs.[2] Currently, GM practice consists of harnessing DNA and RNA base pair sequence information and translating this into medical practice; it is already having a great impact on clinical research practices. In 2011, more than 35 clinical trials used GM practices to advance clinical research projects. Since then, there has been widespread use of gene sequence information in clinical trials by translational researchers. This paper describes how the use of genomic sequencing is having an impact on clinical research, its achievements, challenges and future prospects for advancing clinical trials, based on the article "Genomic sequencing in clinical trials".[1]

Genomic sequencing roles in disease diagnostics and treatments

GM practices use DNA typing and sequencing technology for disease analysis, which provides researchers with the ability to map risky or mutated genes to specific diseases and health conditions.[3] The use of genome sequencing analysis to detect and treat diseases; can have a great impact on the clinical trials process described by Mestan et al.[1] From these authors' perspectives, GM practices allow the integration of gene-processed information in disease treatment, revealing the mechanisms of adverse reactions resulting from drugs interacting with genes for example.[1,3] The study of the genome has already revealed several genes that may be implicated in disease etiology and has brought a new way of studying and treating diseases, as GM enables researchers to investigate with more scrutiny the impact that gene mutations, genes-gene interactions and gene-environment interactions have on disease development and treatment.[3,4]

The sequencing of DNA and RNA base pairs has permitted us to better understand the impact of genetic mutations resulting from changes in the order of base pairs.[1,3] Usually, gene reactions with biological and environmental factors create the conditions for gene mutations, which may predispose an individual to certain diseases or shield that individual from disease.[1,5] For example, individual carriers of CYP2A6 genetic variants that encode an enzyme that metabolizes nicotine may be susceptible to nicotine dependence; on the other hand, carriers of mutant variants, which have a change in the nucleotide sequence and cannot metabolize nicotine, are less likely to smoke.[5] In addition, CYP1A1 genes variants interact with tobacco chemicals to generate lung cancers.[6] In light of these recent findings, Mestan et al.,[1] believe that GM will advance clinical research in the future.

Clinical research using genomic sequencing

The process of incorporating GM in clinical trials has already started. In 2011, specific clinical trials had been designed to use GM's translational practice. More than 35 clinical trial sites have used genomic sequencing technologies to conduct studies on health and diseases.[1] The sponsors of these clinical trials have posted profiles on ClinicalTrial.gov, where the National Institute of Health (NIH) provides the public with information on all clinical trials currently in progress.[7]

These clinical trials started using genomics sequencing methods to understand genetic predispositions to drug reactions. Study methodologies involved laboratory analyses of blood/or lymph, cancer/neoplasms and immune system diseases. These clinical trials have focused on cancer biomarkers studies, investigating diseases such as leukemia/lymphoma, congenital syndromes, central nervous

system disorders and HIV/AIDS. These 35 clinical trials are some of the earliest pioneer studies to have incorporated GM practices in their disease research methodologies by using multiple DNA and RNA sequencing technologies.[1]

Genomic medicine contributions to clinical research studies

Genome-sequencing platforms have revolutionized and enhanced clinical research by integrating new ways of getting information on drug development and patient diagnostics.[1] These platforms process gene sequences and provide information about the order of DNA and RNA base pairs and all the changes that occur inside the nucleosome that may help to analyze disease etiology.[3] The process consists of analyzing genes from the tissues of people with certain diseases and comparing their DNA and RNA patterns with those of healthy individuals, taking into account other possible parameters (e.g. age, gender) and using this process to diagnose patients that exhibit similar symptoms.[1] The same procedure is also used to predict the development of health conditions based on the inheritance of risky genes.[1,3]

These platforms can be divided into first generation (i.e. Sanger) and second generation sequencers (i.e., Next Generation Sequencing), which process smaller and more complex genomes, RNA, copy number variation of genes (CNV) and so on.[1,3] Sanger DNA sequencing technology was coined the "first generation sequencing" platform, because it has been developed as a rapid and cost effective functioning as multi-channel capillary DNA sequencing system in the 1990s increasing the capacity of human DNA sequencing from thousand to millions base pairs.[8] The next generation sequencing (NGS) platforms are the latest DNA sequencing technologies to be introduced, such as Roche 454, Illumina Genome Analyzer (GA) and Applied Biosystems (ABI) SOLiD which are more rapid and cheaper that Sanger.[1] The use of these methods in clinical trials is facilitating the analysis of patients who may have specific gene variants predisposing them to diseases or to adverse reactions to experimental drugs. The application of GM practices is enhancing drug development through the pharmacogenomics process, analyzing drug reactions with genes to generate new drugs that have fewer side effects.[1,4]

The limitations of genomic medicine

GM process has many limitations, because it involves heavy computational data analysis, comparing multiple high volume datasets. GM studies are also limited by a lack of sample size determination in the study design (which is important for epidemiology and statistical analysis). Mestan et al.,[1] recognized that these first generation and next generation sequencing platforms can also fail to detect small polymorphisms that may mislead clinical analysis.[1]

Proposed solutions

To solve problems associated with data processing, innovative bioinformatics approaches to data analysis are used in combination with genetic epidemiology. Genetic statistics may help to reliably process and validate data for translational analysis to improve the outcome of clinical research.[8] Clinical trials should adopt electronic medical record technologies, which use data mining algorithms and can correlate clinical data with variables in clinical studies.[1] All these changes will require clinical staff to be trained in basic genomics, bioinformatics and biostatistics.[3]

Conclusion

Mestan et al.,[1] stated, "Given the unique nature of genomic sequencing research, individuals and groups engaging in GM use in clinical trials may benefit from human subjects training in these specific areas.[1] However, it is apparent that better-defined consensus standards are still needed both nationally and internationally to prepare the growing number of researchers in this field". Their statement illustrates how slowly GM practices are being introduced in clinical research due to the limitations of GM and the challenges researchers face when using GM practices. Despite this, the authors predict that GM would contribute positively to good clinical practices. GM practices have a promising future and may revolutionize the process of clinical trials by shortening the period of drug development, producing drugs that may have fewer adverse reactions and reducing the high cost of clinical trial research.[1,4]

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Conflict of interest

The author declares no conflict of interest.

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