New Stages for Personalized Healthcare Ushered by the Human Genome Project

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Abstract

Personalized healthcare pays attention to individuality, which represents a great opportunity to optimize individual health by adapting to the genomic and environmental contributions to individuality that define personal potential. This article classifies the evolution of the relevant medical informatics which has evolved from simple gross health status, to application of diagnostics for improved selection of therapy, to the production of niche therapies and a new definition of individualized goals. That evolution provides different stages for personalized healthcare that pose a new realm of challenges for the future of medicine.

Keywords: Human genome; Personalized healthcare; Pharmacogenomics; Epigenetics

Introduction

Personalized healthcare describes attention to individuality. In 2016 the average number of people per family was 3.16, but we have never encountered a family with 3.16 people. Analogously, standard of care is not necessarily ideal for an individual patient. For the sake of this argument, the author opines that strict application of standard of care, while a sensible starting point, achieves only half of the maximal potential benefit of healthcare. We are all genetically and environmentally unique. Personalizing healthcare to accommodate individual differences in nature and nurture can offer finer tuned health achievements. This article proposes a model of the history of personalized healthcare framed as 5 different stages, based on the shifting paradigm of relevant informatics.

Discussion

Stage zero of personalized healthcare consisted simply of adjustment of therapy based on individual status, for example, changing the frequency and severity of bloodletting based on exam findings.

Diagnostic progress led to stage one of personalized healthcare, patient selection for more appropriate matching of therapy to medical condition. For example, current use of bloodletting is largely limited to management of too much production (polycythemia) or too little clearance (hemochromatosis), and is no longer used to remove poorly defined “bad humors.” However, before dismissing these stages as obvious and outdated, consider the mismatch of findings and treatment evident in the persisting frequency that antibiotics are prescribed for viral illnesses as well as for exacerbations of inflammatory conditions. Stage one of personalized healthcare, matching treatment to illness, remains underachieved.

The human genome project [1] sparked invention of fast and efficient methods to fully identify the template for individual genetic design, thereby delineating the blueprint for all of the human structural and functional proteins, as well as individual differences [2], at the genetic prescription level. The human genome project realized the ability to map the design and structure of the proteins responsible for human biology structures and function, and also led to fast inexpensive methods to map the genome of individual subjects.

An early major benefit from the human genome project is its tremendous facilitation of the design of new drugs that specifically regulate many of the protein products coded by the human genome [3], a new generation of medications that include “biologics.” Biologics are biologically derived medications which may include activators and inhibitors of biological proteins.

Thus the human genome project ushered in a new stage of personalized medicine, which we’ll call stage 2 of personalized medicine, targeted pharmacogenetics, by providing a widened array of treatment options that may be better matched to individual need and response. The dramatic increase in choice
and specificity of treatments justifies credit of biologics as a new stage in personalized medicine.

However, the human genome project is already providing more, which we'll label as multiple branches of stage 3. Stage 3 of personalized medicine applies the individual's genome to guide diagnosis, treatment and monitoring [4].

Stage 3A applies individual genomics as information support for decision making, by identifying predilections to disease, and inapplicability of some treatments. Stage 3B adds custom design of medications tailored to the individual's structural and functional proteins, for example, to supplement deficient functions, or to combat a specific cancer while sparing the rest of the patient.

Herein, we propose a stage 4 which will utilize the individual genome, plus assessment of individual gene expression and individual post production modifications, to modify the analysis of patient status and response to therapy for meta-analysis of lab results to produce a new layer of lab report assisting interpretation of the confluence of results in relation to the individual. In other words, stage 4 will personalize targets of therapy in relation to a new definition of “normal,” based not on the general population, but rather on the individual's genetic constitution, taking into account modifications of expression due to environment, behavior, disease, and therapy. Steps towards stage 4 include "predictive biomarkers" which look at changes in the expression of genomic products as indications of treatment response [5]. Stage 4 poses a challenge to biometrics and bioinformatics to encompass the full scope of advances in genomics and epigenetics [6].

**Human Genome Project**

The human genome project successfully coordinated multiple laboratories to delineate fully all of the coded sequences in genes that specify the sequence of amino acids that build every protein in humans [1], known as “whole human genome sequencing.” The Genome in a Bottle Consortium, a public-private-academic consortium hosted by the National Institute of Standards and Technology (NIST), develops reference standards, methods, data and disseminates information to facilitate translation of the accomplishments of whole human genome sequencing to clinical practice and personalized healthcare, by “authoritative characterization of human genomes for use in analytical validation and technology development, optimization, and demonstration” [6].

“Understanding the causes of cardiovascular diseases logically starts with the genetic code that specifies the designs for the structures and function. These may be inherited from your parents, or may differ from either parent due to spontaneous mutations. Congenital heart disease comprises many different abnormalities, primarily of structure. For example valves and tubular pathways may be malformed, and connections may be deviant. Connections not normally present are known as shunts. The completion of the human genome map was a major accomplishment enabling complete enumeration of all the possibilities. Genes specify the codes for gene products that make the structural elements, signals, receptors and other building blocks that establish health and disease. However, the complete genome map is just a stepping stone, as it does not completely explain why, where, or how the gene products are regulated and interact. Epigenetics picks up on the issues of gene expression, product modifications and assembly. Epigenetics is the scientific focus that characterizes the vital follow-on steps from genetic code to the determination of structures and function of the cardiovascular and other biologic systems” [7].

**Biologics and Pharmacogenomics**

Biologics are pharmaceutical products manufactured, extracted from, or derived at least in part from biologic sources. A growing number of biologics are produced from genetic code segments corresponding to a human natural gene product or a modification of it to increase or decrease its functional roles or change its distribution or immune responses.

Current usage of the term biologics generally focuses on medications acting as bioactive substances that may be administered as pills, injections, or application on the skin or under the tongue, thereby excluding other biologic derivatives such as foods, soap, and gelatin. In current use, the term biologics is further restricted to protein and/or nucleic acid based products modified from sequences coded in the human genome, excluding other biologic extracted products such as blood, hormones, body part transplants or vaccines. As production techniques evolve, the distinction between biologic derivation and bench synthesis of products based on or related to structures coded in the human genome may become blurred. The term “genomics” has other meanings, perhaps a better term will be genomic products or genoproducts. The development domain is termed pharmacogenomics [8].

**Epigenetics**

The impact of the human genome does not depend solely on the chromosome DNA code sequences for protein construction. Additional factors include DNA methylation, which can modulate gene expression. Histones in chromatin can form heterochromatin to deactivate the DNA transcription required for gene expression. RNA can interfere with DNA transcription. Post transcription modifications, also influence gene expression. Environmental factors such as food abundance at critical periods in growth and development may affect these modifiers [9]. All of these factors participate in the development of genomic and epigenetic biometrics.

**Regulation**

There is a risk that the greatly expanded test combinations and definitions of the new normal for stage 4 of personalized healthcare will be overwhelming. The former commissioner [10]
of the Food and Drug Administration (FDA) has called attention to that as yet resolved issue. “I think the community better take this really seriously,” said Robert Califf (cardiologist and former Commissioner of FDA), discussing Laboratory Developed Test (LDT) regulation, at the 12th Personalized Medicine World Conference at Harvard. While, on the one hand, regulation shouldn’t stifle innovation, he noted that doctors can’t be left to figure out which test they should order. “We’ve got to come up with some middle ground, so regardless of where you are in the US you can get a reproducible laboratory result” [11].

Conclusion

Personalized healthcare recognizes that the uniqueness of individuals corresponds to an opportunity to tailor therapy to individual needs. The informatic basis for personalization corresponds to distinct stages in the evolution of personalized care. Stage zero consisted of adjusting “one-size fits all” therapy to the physical status of the patient. Stage 2 utilizes diagnostics for selection of therapy. Stage 3 applies pharmacogenomics to develop individual specific therapies. Stage 4 will redefine “normal” and targets of therapy based in the individual genome, gene expression, and epigenetics. The future of medicine will require regulations that hopefully will strike a good balance between restrictions of chaos and fulfillment of this potential.

References

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