# PRECISION MEDICINE: UNDERSTANDING THE BOTTLENECKS

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OPINION

HIGHLIGHTS

Precision medicine is the holistic management of health and wellbeing at a personal level with a high degree of precision dictated by the state of the art technology. Biggest bottleneck in the progress of precision medicine is computational. Long term investment in fundamental sciences such as mathematics, physics and chemistry is required to develop better computers, materials and equipment required to make progress in precision medicine.



## ABSTRACT

Precision medicine aims at the management of diseases and wellbeing with precision at a molecular level taking into account genetic and epigenetic variations at a personal level. Several of our disease management strategies lack precision. We try to manage symptoms instead of rectifying the fundamental issue which causes the pathology. For example in common diabetes we try to control blood glucose levels instead of finding and treating the root cause of diabetes which could be different from person to person. What prevents precise understanding and precise drug development strategies are our limitations in analysing and interpreting genomic, proteomic and metabolomics data. Our inability to model the three dimensional structure of proteins, protein - protein and protein-small molecule interactions, signalling pathways and their complex cross talks is a big limitation. Therefore one of the biggest bottlenecks for precision medicine is computational. The only way towards progress in personalized medicine is long term investment in basic sciences such as mathematics, physics and chemistry which would help us to build better technologies for better computers, materials and imaging equipment. It is high time to alert the Federal and State governments and the corporates about the importance of investing in research projects with ultra-long term goals.

KEY WORDS: *Drug selection, computational diagnosis, socio-economics in precision medicine*

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## EXPERT OPINION

Precision medicine is about the prediction, diagnosis and management of health and wellbeing with an increasingly greater precision which takes in account the heterogeneity of human genetic and epigenetic landscape, the environment and life style in a holistic way. In the literature, there are instances where precision medicine is used interchangeably with personalized medicine, in the context of "tailor made" management which is distinct for each individual.

Currently most of our treatment strategies are not focused at the root cause. For example the way we treat diabetes is analogous to "treating fever with paracetamol", an antipyretic nonsteroidal anti-inflammatory drug. This is because; fever can be the result of several pathologies such as influenza virus infection, a bacterial infection of the gut, an amoebic liver abscess, autoimmune inflammation of pancreas, ingestion of organophosphate pesticides or exposure to certain metal fumes or cancers (such as non Hodgkin's lymphoma) [1,2]. In most cases, paracetamol may decrease the fever irrespective of what caused the fever. This is a symptomatic treatment which means we are 'treating' the symptom rather than the cause. The same is true with the treatment of diabetes mellitus type 2 (DMT2), the common diabetes or fatty liver disease -another major public health problem, to a great extent. Defects in genes involved in insulin receptor signalling, nuclear receptor signalling, dysfunctional adipose tissue, mitochondrial defects possibly result in DMT2 (or fatty liver) [1].

There are hundreds of mutations and several thousand permutations and combinations of these mutations which results in diabetes, a disease which is often remembered and treated for the 'raise in blood glucose level' beyond certain arbitrary values accepted by one or the other professional bodies [1]. Raise in blood sugar is in fact only one of the several 'signs' of DMT2. This is the way we manage most of the diseases in 'modern medicine' with certain notable exceptions, for example the use of antibiotics against certain infections. Another notable example from this decade is the use of' imatinib' an example of a designer drug used in the treatment of multiple cancers, most notably Philadelphia chromosome-positive (Ph+) chronic myelogenous leukaemia [3]. This is a drug we humans designed against a disease with an insight into the molecular pathology with certain degree of precision. Few other diseases in which precision medicine is successful (or tried!), based on the genomic signatures include breast cancer and HER2 status, EGFR therapy based on K-ras wild type versus the mutant in colorectal and/pancreatic cancer (despite the tumours appear similar for the pathologist's eye !).

### *Computational Bottleneck*

However, in order to make further progress we need to know a lot more. 1) Association of genes with diseases. A great deal about the mutations, SNPs, polymorphisms 2) Interactions between genes and gene products- the intricacies of cell signalling pathways and their cross talks 3) Precise three dimensional modelling, structure and interaction prediction of peptides and proteins 4) Newer ways to design and synthesis proteins and small molecules in large scale. We are still taking baby steps in these areas. One of the great challenges faced by humanity is the huge conformational possibilities of peptides and proteins under different physical and chemical conditions [4, 5]. This is by and large a computational challenge. Therefore one of the major bottle necks is our computational limitation. We need to invest heavily on the fundamental advancement of computational technologies such as quantum computing and neuromorphic chips. It may be noted that the analysis, interpretation and storage of 'big data' is only one small edge of this polygon [7].

### *Bioengineering and Imaging Bottleneck*

Precision medicine is not only about drugs and genes as many believe. It extends to advanced biomaterials, imaging techniques, nanotechnology etc. This is important because many diseases cannot be solved by precise drug molecules alone [5, 6]. Precise delivery is also important. In many cases a precise cure can be achieved only by precise removal or transplantation of a cell or its organelles. This is especially true for neurodegenerative diseases as well as 'natural' ageing. Precise identification and removal of damaged neurons or repair of neuronal connections require imaging technologies with high resolution and precision. The physical removal might require precision drug delivery system or 'nano surgery'. In order to achieve all these we require more robust technology and this in turn require several quantum jumps in fundamental sciences namely mathematics, statistics, physics and chemistry [5,6].

### *Financial Bottleneck*

The cost of genome or epigenome sequencing is going down year after year probably following the Moore's law. The cost of the Human Genome Project was about $3 billion in 2003. Now one can get entire human genome 'sequenced' in $1000 in 2016 [8]. This is the cost for 'sequencing'. The real cost is in analysing terabytes of data generated by sequencing. This requires extensive computational and manpower (although we can expect more and more manpower being replaced by computers as they become closer and closer to human intellect). It is needless to emphasis the enormous financial gap which is evolving as a major bottleneck in the advancement of precision medicine.

### *Social Bottleneck*

This is one of the major bottlenecks which would surface in the future. Social bottleneck is a new moon in the horizon. This will start from privacy issues, health insurance and employment issues and extend to the issues which would be brought in by genome editing at a personal level and in the backdrop of human evolution.

### *Long-term Investment in Fundamental Sciences is needed for the Progress of Precision Medicine*

Quantum jumps in precision medicine can be achieved only through the development of advanced technology and this can be achieved only through quantum jumps in basic sciences such as mathematics, physics and chemistry. This definitely requires increased investment in fundamental research [5]. This kind of research, which may not give any immediately 'useful 'output, will take precision medicine to its 'dream destination'. It will take several decades. Private companies, corporates and investment firms will not be interested in such kind of long term investments and therefore it is the duty of the governments to invest in fundamental research with a long term vision [5, 9]. However, there some of hope from the corporate sector, for example, Google is funding some research projects with long-term goals.

## CONFLICT OF INTEREST

The authors declare no competing interests.

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## FINANCIAL DISCLOSURE

None.

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