

# The genomic and precision medicine in clinical practice- Current perspectives and future directions

## Abstract

An important milestone in the history of medical science is the recent completion of the human genome sequence. The progress on identification of approximately 22,000 *homo sapiens* genes and their regulatory regions provides the framework for understanding the molecular basis of disease. This advance has also laid the foundation for a broad range of genomic tools that can be applied to medical science. These developments in the gene and gene product analysis across the whole genome have opened the way for targeted molecular genetic testing in a number of medical disorders. This is destined to change the practice of medicine.

The future clinical practice will be more focused, precise and individualized, often referred to as “precision and personalised medicine.” However, despite these exciting advances, many practicing clinicians perceive the role of molecular genetics, in particular that of medical genomics, as confined to the research arena with limited clinical applications. Genomic medicine applies the knowledge and understanding of all genes and genetic variation in human disease. The basic ingredient of the contemporary practice of medicine is clinical molecular medicine that encompasses genetic, genomic, and molecular applications. This article introduces genomics-based advances in personalised disease-susceptibility screening, diagnosis, prognostication, stratified approach for genomics-led therapeutics, and prediction of treatment outcome in various areas of medicine.

### Key words:

Human genome; genome sequencing; genome variant; genomic medicine; precision medicine; personalised medicine; evidence-based medicine; stratified medicine

## Introduction

Recent innovations and new developments in molecular biology, biotechnology, genomics, and many other *OMIC* sciences have revolutionised the contemporary and future practice of clinical medicine. The diagnosis of most complicated and rare conditions is now possible with high degree of precision. The “gene-specific” and “genome-driven”

diagnoses in many inherited and genetic disorders are now possible. The understanding of molecular mechanisms in a number of common and complex medical conditions has vastly improved. Progress in targeted genetic and molecular approach in pharmacotherapy has led many improvements from the current therapeutic regimens, which are designed for the “average model patient” and “one-size-fits-all” model approach. However, this has changed

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dramatically with rapid advances made in evidence-based precision and personalized medicine [1]. The whole process in the practice of genomic and precision medicine involves a stepwise approach in building the holistic picture referred to as stratified medicine with the ultimate aim of individualized or personalized therapeutic interventions [2]. The scope and limitations in the new exciting field of stratified and personalized medicine are reviewed in this article.

During the last decade, new genomic diagnostic tools and molecular innovations have led to the emergence of precision medicine, an innovative approach to disease prevention and treatment, which takes into account individual differences in people's genes, environments, and lifestyles. The precision medicine is central to stratified and personalized medicine. It provides the clinician with tools to better understand the complex molecular mechanisms underlying a patient's health, disease, or condition, and to better predict which treatments will be most effective. Advances in precision medicine have already led to powerful new discoveries and several new treatments, which are tailored to specific characteristics of individuals, such as a person's genetic makeup, or the genetic profile of an individual's tumour. This is leading to a transformation in the way we can treat diseases such as cancer. Patients with breast, lung, and colorectal cancers, as well as melanomas and leukaemia, for instance, routinely undergo molecular testing as part of patient care, enabling physicians to select treatments that improve chances of survival and reduce exposure to adverse effects [3]. The potential for precision medicine to improve care and speed up the development of new treatments has only just begun to be exploited. Translating initial successes to a larger scale will require a coordinated and sustained global effort. Through collaborative public and private partnerships, the stratified and precision medicine initiatives will harness advances in genomics and biotechnology for accelerating biomedical discoveries [4]

### Genetic, genomic, and molecular revolutions in medicine

Following the phenomenal discovery of the structure of the nucleic acids (DNA and RNA) and subsequent sequencing of the human genome, rapid progress is continually being made in understanding the genetic and molecular bases of human disease. In early stages the focus was largely on the peptide molecular basis, for example, deciphering the structure of haemoglobin molecule to unravel the complexities of a number of inherited and acquired blood diseases. This period was the hallmark of molecular medicine. Nevertheless, developments in Mendelian genetics (single-gene diseases) facilitated understanding of the causation of human disease in the context of genes, inheritance patterns, recurrence risks, and genetic counselling [5]. However, these advances and evolving trends in medicine were restricted due to limited laboratory diagnosis. The practice of clinical molecular medicine in genetic and genomic terms is now a reality and most clinicians are emerging with new skills and

competencies. This juncture changed dramatically with the sequencing of the human genome, opening new horizons for clinical medicine and even extending into domains of public and population health [6].

Although only less than 1% of the human genome sequence is different in any two individuals, variable nucleic-acid coding or noncoding sequences in the remainder of the genome could be functionally relevant to individual's genetic constitution or genomic signature [7]. The "personalized sequence variation" is undeniably important and is agreeably the fundamental basis of genomic medicine. Functional annotation for individual sequence variation, when complete, will be crucial in precision diagnosis and personalized therapeutics [8]. This is likely to be vastly improved with the availability of targeted sequencing of selected genes, exons, or promoters.

Currently, the focus is on whole-genome sequencing (WGS) that should reveal a full range of variants in both coding and noncoding genome. Variants that cause amino acid changes, and thus altered protein product, are in general dissimilar (nonsynonymous) compared to those that lack such an association (synonymous). If an excess of nonsynonymous substitution is observed for one particular coding region then this can be taken as an indicator of diversifying (positive) selection. With the help of next-generation sequencing technologies, more and more variants are being characterized and sequence annotations made available. It is envisaged that ultimately a fuller picture will emerge of the variants that alter genome function and will enable selection of those that contribute to health and disease in a particular individual [9].

During the last decade, rapid and unprecedented progress has been made in applied and translational genomic research leading to practical and dynamic utilizations in clinical medicine. Complicated laboratory techniques of genome sequencing (whole-exome, targeted deep-capture, and whole-genome) are no longer confined to research settings [10]. With the advent of next-generation sequencing the speed of generating enormous genome sequencing data is considerably greater at successively lower costs [8]. An individual may get personal genome sequenced at around £500. Clinical diagnostic requests are now routinely made for array-comparative genomic hybridization (aCGH), clinical whole-exome sequencing (CWES) and whole-genome sequencing (WGS) by the broad range of specialists and general medical and health practitioners or even directly by the consumer [11,12]! Sincere efforts are put in place, both in public and private sectors, for establishing the role of genome sequencing in clinical medicine and public health.

Higher state-level commitments are declared to set standards and guidelines for the genome sequencing in both clinical and research settings. The recent 100,000 genomes project of the UK government is a good example. The project, now aimed at 5 million genomes, offers a unique opportunity for bridging

the gap between innovations and clinical applications, whether state or privately funded. In the context of “precision and personalized medicine,” genetic, genomic, and molecular laboratory techniques are now being increasingly applied to select patients based on specific genetic and molecular signatures for a clear unambiguous diagnosis and selection of drugs pertinent to a particular therapeutic regimen. This approach requires properly validated scientific and clinical evidence at multiple levels within the agreed algorithm. The stepwise manner or stratification of the whole process has gained recognition and momentum in recent years leading to the emergence of “stratified medicine,” an umbrella term to encompass multi-disciplinary physicians, clinical scientists, and healthcare professionals. The core aim of these emerging concepts remains “precision diagnosis and management tailored to individual’s needs.” Thus fundamentally the stratified medicine offers the system for precision medicine, which implies that an individual patient’s clinical care is based on specific risk of disease or response to therapy by using diagnostic tests or techniques, whether conventional or

genetic [13]. The whole model is set in the background of personal lifestyles, the structure and function of the family, sociocultural variation, ethnicity, and the community at large (Figure 1). This model is beginning to yield dividends for patients and healthcare providers from targeted and effective treatments, whereas industry benefits from the potential for more efficient therapeutic developments as well as the market expansion for novel therapeutic drugs and devices.

The development of stratified medicine based precision and personalized medicine is now pursued globally. To most medical and health practitioners the concept and philosophy behind “stratified medicine” are not unfamiliar. However, this approach is now remarkably strengthened with increasing accuracy and sophistication of the genomic and molecular medicine. It is widely acknowledged that the power of precision and personalized medicine is considerably enhanced with the availability of individual genome-sequence information [14].

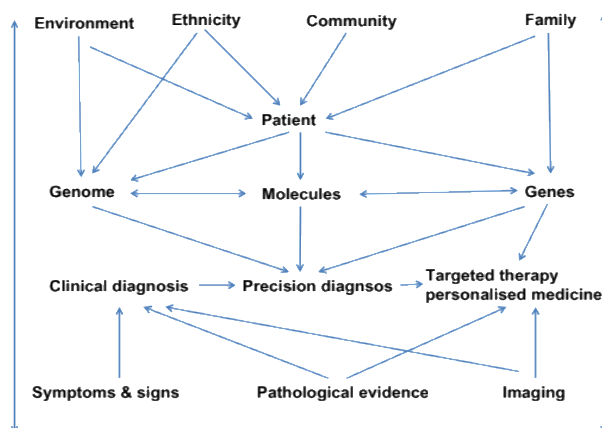


Figure 1: The model of integrated genetic, genomic, and molecular medicine based on individual clinical evidence in the background of personal lifestyle, family history, ethnicity, sociocultural variation, and the community at large.

**Evidence-based, precision, and personalized medicine**

The success of genomic and precision medicine will depend upon the ability to sequence an individual’s full genome. With the benefit of new technologies, it is possible to generate giga bases of data as short sequence reads and to assemble the data accurately using the finished sequence as a template. This will provide the essential database of human genome variation for a given population. Comparison of these data sets will provide a full profile of common genome variation along each chromosome. Detection of each variant will help in estimating the recombination rates and correlation along each chromosome. This approach could give important baseline information on healthy tissue compared to

pathological tissue. For example, a comparison of the cancer-genome sequences could allow monitoring the DNA changes on a genome-wide basis for cancer development. A similar approach could also be applied for other diseases. This genomic information on both healthy and diseased tissue could be used in screening an individual’s disease risk and devising appropriate therapy and medical advice, paving the way forward for personalized medicine (Figure 2) [15].

As the human genome functional annotation becomes available, the prospects of “personalized medicine” will improve. A hypothetical scenario is described [16], where variation in the PPAR-γ gene, one of the susceptibility genes

in type 2 diabetes mellitus (T2DM), is employed in selection of the most appropriate oral hypoglycaemic drug.

The use of personal genetic information in a clinical setting could be requested and consented by the individual concerned. The individual sequence acquired could be restricted to one or two genotypes or as much as a complete genome sequence. The information thus acquired would be exclusive and private and wholly owned by the individual. It could be stored electronically, protected by a high-security code requiring unique personal identifiers, such as used for storing multiple fingerprint or iris pattern, for access only with the consent of the individual. The information might be taken either before consultation or afterwards and in either case would be subject to counselling by the medical practitioner and consent by the individual. The clinical consultation could initiate a specific investigation. The personal annotated genetic information, such as a set of gene mutations or variants for cardiovascular disease, of the individual patient would be made available for interpretation with respect to the clinical phenotype. The clinician would use the available risk information concerning each variant to provide a genetic assessment for the individual. In the case illustrated the individual has the heterozygous genotype TC at position

3:12,450,610. This corresponds to having both Pro 495 and Ala 495 forms of the protein PPAR- $\gamma$ .

This genotype confers an increased risk of insulin-resistant T2DM on the individual and also resistance to the thiazolidinedione class of antidiabetic drugs. Combining this with risk information for other genotypes would help to make informed subsequent clinical decisions. Thus with easy access to a well-annotated human genome and availability of cheap, accurate WGS technology, an individual could acquire either a specific or complete genetic-health profile, including risk and resistance factors. The information could then be used to improve and guide important medical decisions, to assess the risk of possible future exposures, and to select preventive treatments for improved health [16]. In brief the practice of personalized or specifically individualized medicine will become the central focus of the future practice of clinical medicine. However, this will demand a lot of commitment, perseverance, and investment at personal, family, community, and public or state levels. Inevitably and understandably, this approach will raise several ethical and social concerns for the fear of inequity, discrimination (primarily due to enormous costs and affordability), and potential misuse or abuse (malpractice).

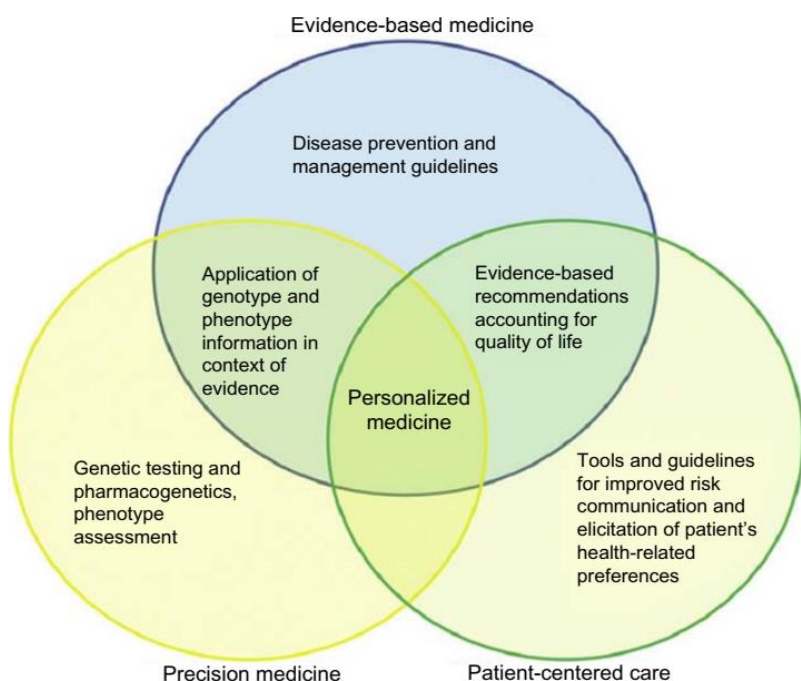


Figure 2: Integrated relationship of personalized medicine with evidence-based medicine, precision medicine, and patient-centred health care. Adopted with permission from Kang SK et al. A road map of personalized care in radiology. *Radiology* 2015;277 (3):638!43.

The practice of personalized medicine shall not be allowed to develop without relevant professional and statutory safeguards put in place. This approach should be one of the other major ingredients of clinical practice pathway, what is often referred to “the 4 Ps of medicine”: medicine that will be more precise, predictive, personalized and pre-emptive

[17,18]. Along with this list additional new elements of preventive, preparatory participatory are also added (Table 1). To achieve these key long-term goals, National Institutes of Health (NIH-USA), National Institute of Health Research (NIHR-UK), and many other global organizations (Global Alliance for Genomics and Health, GA4GH) are actively

pursuing and promoting research in the aforementioned areas. These organizations are strategically investing in research to further our understanding of the fundamental causes of diseases at their earliest genetic, genomic, and molecular stages. The central theme of personalized medicine is based on the simple basic concept that individuals respond differently to environmental factors including therapeutic interventions, according to their genetic/genomic endowment and their own behaviour and lifestyle. In the future, applied and translational genomic and molecular research will allow us to predict how, when, and in whom a

disease will develop. We can envision a time when we will be able to precisely target or stratify treatment on a personalized (individualized) basis to those who need it, avoiding treatment to those who do not. Ultimately, this individualized approach will allow us to pre-empt disease before it occurs, utilizing the participation of individuals, communities, and healthcare providers in a proactive and preparatory fashion, as early as possible, and throughout the natural cycle of a disease process [18,19].

Table 1: Acronyms of personalized genomic medicine and health care [17].

- Precision diagnosis
- Personalized information and counselling
- Personalized targeted therapy
- Pre-emptive approach
- Prediction and prevention of complications
- Preparatory and targeted planning for long-term health surveillance and care
- Participation in long-term management through lifestyle and behaviour modifications



Figure 3: Clinical pathway model for genetic/genomic diagnosis and cascading results in close family relatives for targeted health surveillance and preventive action. Source: Adopted with permission from Barwell et al. Challenges in implementing genomic medicine: the 100,000 Genomes Project. J Transl Genet Genom 2018;2:13; doi: 10.20517/jtgg.2018.17.

**The stratified medicine**

“Stratified medicine” is the process of grouping of patients based on risk of disease or response to therapy by using diagnostic tests or techniques [13]. Patients and healthcare providers both benefit from more targeted and effective treatments, whereas industry benefits from the potential for

more efficient therapeutic development as well as the market expansion for these new treatments. The development of stratified medicine is being pursued globally as its benefits are increasingly recognized. The concept and philosophy behind “stratified medicine” are not unfamiliar. However, this approach is now remarkably strengthened with increasing

accuracy and sophistication of the genomic and molecular medicine [22]. Stratified approaches to therapy are expected to become the standard for the management of a whole range of diseases (e.g., chronic heart failure) provided that these match certain

criteria as recommended by leading clinicians and scientists [23]. The Academy of Medical Sciences in the United Kingdom ([www.acmedsci.ac.uk](http://www.acmedsci.ac.uk)) has recommended criteria for stratified medicine (Table 2) [24].

Table 2: Criteria for stratified medicine (The Academy of Medical Sciences, United Kingdom) [19]

1. Continued research to understand the genetic and molecular bases of diseases
2. Development and use of increasingly sophisticated and powerful informatics technology
3. Improvement and standardization of clinical data collection and linkage with genomic and other databases
4. Increased collection of tissues for biomarker research and evaluation, and its organization in national and international biobanks
5. Greater efficiency and productivity in the development of therapeutics and diagnostics
6. The introduction of flexible and novel approaches for the regulatory assessments of innovative stratified medicine products
7. Improved flexibility in pricing for stratified medicine products—both for the diagnostic and for the associated therapy—to ensure cost effectiveness for payers while encouraging innovation

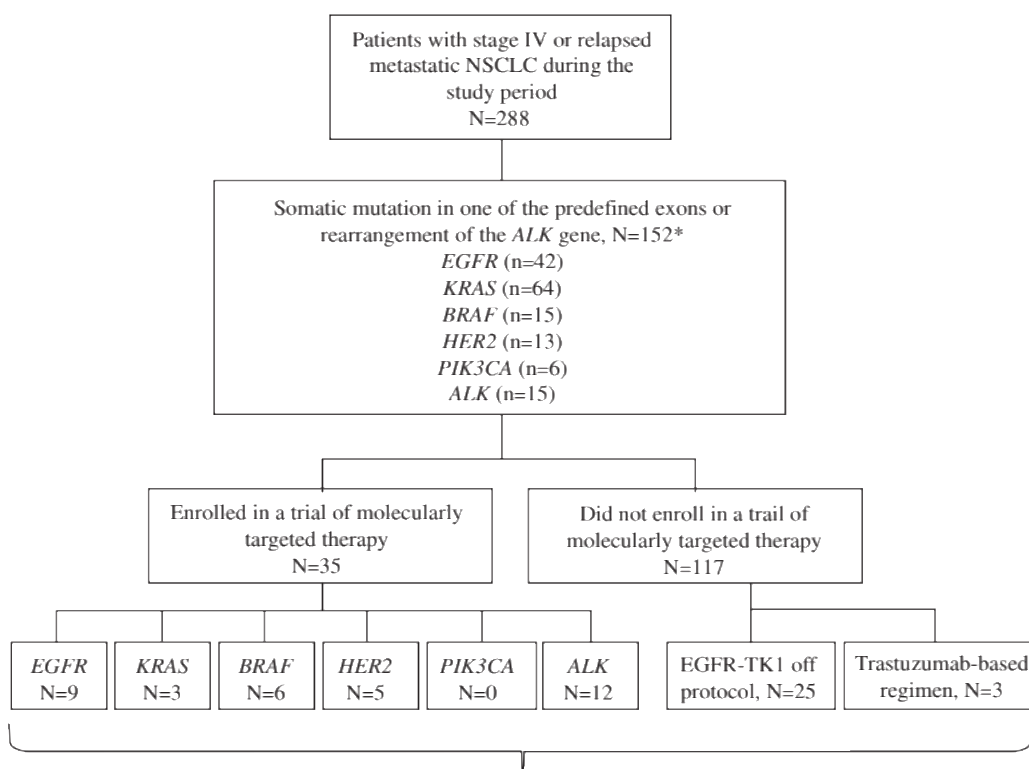


Figure 4: Flowchart of patients with stage IV or relapsed metastatic NSCLC onto molecularly targeted therapy during the study period [26]. [NSCLS- Non-small cell lung cancer].

Several programs and incentives are now operational for “stratified medicine” to enable partnership across academia, industry, healthcare systems, regulatory/pricing authorities, research funders, and patient groups. The progress toward stratified medicine, increasingly confused with “personalized medicine,” relies fundamentally upon data, which is central to the applied and translational research to understand the

molecular basis of disease; development of targeted interventions; effective regulation, health technology assessment, and valuation of stratified medicine products; and the stratification of treatment by physicians [25].

Among many examples of stratified approaches in planning and executing treatment for common cancers, the case for

non-small cell lung cancer is noteworthy, probably the best paradigm in the context of stratified medicine (Figure 4) [26]. Heterogeneity in patients, based on driver oncogene mutations, is crucial for selecting targeted drugs for treatment [27]. There are several challenges and obstacles to realizing the full potential of benefits of the substantial progress in genomic and molecular research in pursuit of stratified approaches to clinical medicine:

- Standardization of genome-sequencing platforms to avoid laboratory-to-laboratory variability complicating the analysis of combined datasets.
- High levels of enrolment for sequencing are required to benefit from the accumulation of whole-genome sequence data, which will require that privacy and data-protection concerns be addressed.
- Because of the complexity, capital expense of equipment, and size of datasets, progress in molecular medicine is increasingly requiring collaboration between many academic groups, public institutions, and industry, often across countries.
- Genomic information on its own, although useful, is only part of the story. Greater knowledge is gained when such genetic information is linked to clinical outcomes. Thus there remains a major hurdle to link genome databases to healthcare records, which need to be electronic for this to be done efficiently
- Research is still required so that genetic variations are not only correlated to diseases, but causal links are established, if the underlying molecular mechanisms of disease are to be understood.
- Correlation of genetic variation and disease may sometimes not transcend ethnic groups. The Pharmacogenetics for Every Nation Initiative has been set up to address this issue.
- The effect of epigenetic variations on drug response and pharmaco-epigenomics needs further research [28]. Epigenetic variations are inheritable, affect gene expression levels and therefore phenotype, and yet do not result from changes in the DNA sequence [29].

#### **Integrated genomic and molecular medicine**

There are multiple factors that will determine the development and adoption of genomic and molecular approaches to medicine (Figure 5). There are “pull” factors, in that the healthcare system needs to become increasingly effective and sustainable, in particular the economic policies

for investment and cost reimbursement. There are also “push” factors, from recent advances in medical science and informatics; and the pharmaceutical industry requires substantial improvements in research and development productivity to remain a viable sector in the long term [30]. These factors accelerate the momentum of stratified medicine and are transformative in the provision of care. Detailed discussion on this aspect of stratified medicine is beyond the scope and remit of this chapter.

However, the following major areas are important to consider for planners and developers of genomic medicine:

- Effective and sustainable healthcare systems
- Scientific and technological advances
- Diagnostic applications to accommodate new disease categories
- Challenges facing the pharmaceutical industry
- Role of the regulatory and statutory agencies

Successful implementation of genomic medicine strategy would depend on dealing with mammoth organizational challenges. The algorithm of a proposed clinical protocol and pathway requires multiagency and multispecialty approach (Figure 5 & 6) [31]. All elements of phenotype recognition, clinical diagnosis, evidence-based genomic and molecular diagnosis, research efforts for annotating and recording all sequence variation information, parallel pilot projects, keeping the health care and public informed, and gaining support from relevant funding sources are all important.

In one of the seminal articles, Khoury et al. [32], emphasised the need for comprehensive research agenda to harness human genome discoveries into health practice in a way that maximizes health benefits and minimizes harm to individuals and populations. A framework for the continuum of multidisciplinary translation research is proposed that builds on previous characterization efforts in genomics and other areas in health care and prevention. The continuum includes four phases of translation research (T1-T4) that revolve around the development of evidence-based guidelines (Figure 5). With continued advances in genomic applications, however, the full continuum of translation research needs adequate support to realize the promise of genomics for human health.

## Multidisciplinary Translational Medicine

*Khoury et al (2007) Genetics in Medicine 7:665-674*

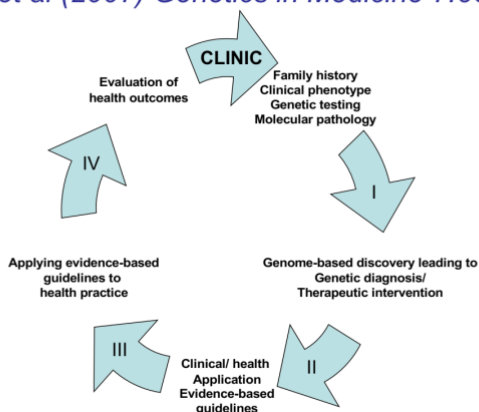


Figure 5: The model of multi-disciplinary translational research for evidence-based genomic medicine [32] Subsequently, Manolio et al. proposed the landscape of integrated genomic and molecular medicine with major components of infrastructure development, research and development, service programs development, audit and quality control, and outcome measures (Figure 5). [32]

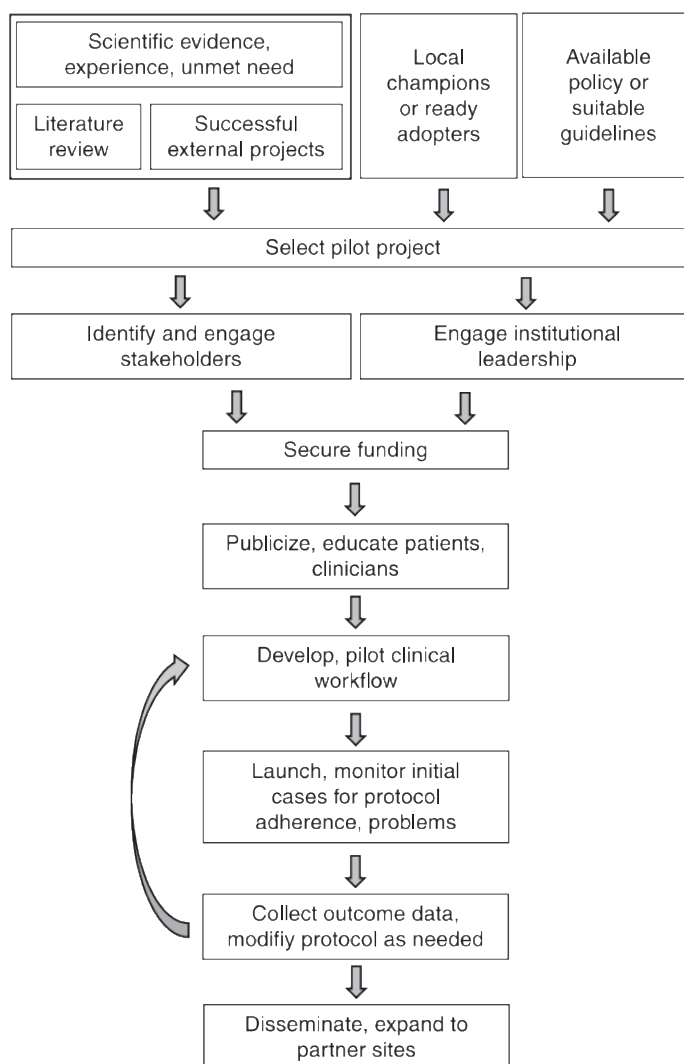


Figure 6: Landscape of integrated genomic and molecular medicine with major components of infrastructure development, research and development, service programs development, audit and quality control, and outcome measures. Source: Courtesy of Manolio et al. Implementing genomic medicine in the clinic: the future is here. *Genet Med* 2013;15(4):258!67.[32]



## The 100,000 Genomes Project

- Launched by former **PM David Cameron** in 2012
- Delivered through a **partnership** between the NHS, Genomics England, NIHR, Public Health England, Health Education England
- Whole genome sequencing NHS patients with **rare disease, cancer and infectious disease**
- Recruitment through **13 NHS Genomic Medicine Centres** – recruiting through routine care, treating through routine channels
- **Involvement of all countries of UK**



Figure 7: The 100,000 Genomes Project of United Kingdom (www.genomicsengland.co.uk). [21]

Finally, the success of the UK 100,000 Genomes Project (Figure 7) is noteworthy to ensure systemic evidence based provision of genomic medicine services in the National Health Service (NHS). It is evident from the enthusiastic response from the UK government to expand the project to include 5 million genomes.

Last not the least, the art and science of the practice of medicine at all times are true reflections of dynamic adjustment of the physical state of the human body and environmental pressures. In this context the innate characteristics conferred by the genetic and genomic constitution provide the framework on which a range of lifetime environmental experiences and pressures would act

and manifest in either positive or morbid (disease) states. The importance of inter-human variation was emphasised by Sir William Osler, the Regius Professor of Medicine (Oxford University, 1892), *“If it were not for the great variability among individuals, medicine might as well be a science, not an art.”* This was later echoed clearly over 100 years ago across the medical community in one of the classic Harveian Orations of the Royal College of Physicians in London, England (Sir Clifford Allbutt, the Oxford Regius Professor of Physic, Harveian Oration, 1900), *“It was in Padua, Italy that medicine, long degraded and disguised, was now to prove her lineage as the mother of natural science, and the truth of the saying of Hippocrates, that to know the nature of man one must know the nature of all things”.*[32]

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