

## THE PATH OF PERSONALIZED MEDICINE: REGULATORY PERSPECTIVE

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### REVIEW ARTICLE

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#### ABSTRACT

Personalized medicine (PM) has become a topic of great interest because of its potential to improve patient care and optimize therapeutic strategy. The way we understand and treat disease is changing rapidly. The traditional form of personalized medicine has been based on the observable manifestations of a disease or treatment, such as a tumour on a mammogram, the appearance of cells under the microscope, etc. But now personalized medicine promises to introduce a new standard of healthcare by using molecular analysis to achieve optimum medical outcomes in the management of a patient's disease or disease predisposition. PM is providing the right treatment, to the right patient at the right time by using modern biology's new methods and tools. The objective of this paper is to focus on a realistic scenario for its evolution, and to explore the issues affecting the development and implementation of personalized medicines and various regulatory pathways involved in its regulation. This paper also highlights the roles and applications of personalized medicine. The success of personalized medicine depends on having accurate diagnostic tests that identify patients who can benefit from targeted therapies. The common goal: an integrated policy framework that balances patient, industry and scientific interests without hindering advancement of this tremendously important sector. Through these efforts, we can help ensure that personalized medicine is able to fulfil its promise as rapidly as possible.

**Keywords:** Pharmacogenomics, Pharmacogenetics, Personalized pill, Targeted therapy.

#### INTRODUCTION

Many of us wonder why some people develop cancer while others do not and why a medication might work well for one person but be less effective or cause serious side effects in another. Although these differences are due to a number of important factors such as age, weight and lifestyle, our genetic make-up also plays a part. Using information about genetic predisposition to disease is a key part of personalized medicine.

Personalized medicine is definitely one of the most exciting topics in medicine today. "**Personalized medicine**" refers to the tailoring of medical treatment to the individual characteristics of each patient. It does not literally mean the creation of drugs or medical devices that are unique to a patient, but rather the ability to classify individuals into sub populations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those

who will benefit, sparing expense and side effects for those who will not. (1)

The goal for personalized medicine must be to move as swiftly as possible toward the identification of individual risk factors, be they environmental or genetic, that play a direct role in disease risk. (2)

The new science of personalized medicine is embodied in an approach dubbed P4 medicine by Institute for Systems Biolo and Dr. Hood, because of its four attributes:

- It is **personalized**; it is based on an understanding of how genetic variation drives individual treatment.
- It is **predictive**; it is able to identify what conditions a person might contract in the future and how the person will respond to a given treatment, enabling the development of a tailored health strategy.
- It is **preventive**; it facilitates a proactive approach to health and medicine, which

shifts the focus from illness to wellness.

- It is **participatory**; it empowers patients to make informed choices and take responsibility for their own health

This last attribute of P4 medicine—patient empowerment—is part of a broader trend toward consumer-focused healthcare, enabled by easy access to health information that was once available only to medical professionals.(3)

## PARADIGM OF PERSONALIZED MEDICINE



**Figure 1: Personalized Medicine Coalition** ([www.personalizedmedicinecoalition.org](http://www.personalizedmedicinecoalition.org))

This arrow reflects the current and anticipated flow of healthcare services, and changing points of intervention, as medicine becomes more personalized. Early detection testing will continue based on large population risk (e.g., mammograms), while new forms of risk assessment will be incorporated (e.g., determining which women carry the genetic variation that increases their risk for developing cancer). Though true prevention must occur before disease symptoms are present, better risk assessment enables more targeted monitoring (e.g., women with the genetic variation should have more frequent mammograms); followed by symptom-driven diagnosis, in which molecular monitoring could possibly identify disease subtypes that cannot be clinically determined. Such diagnosis may or may not lead to targeted therapy but in either event we may also benefit from improvements in monitoring a patient's response to a particular therapy. (5)

## PERSONALIZED MEDICINE TIMELINE

The term »personalized medicine« (PM) was coined in the late 1990s, but was not introduced to general US public until about a decade later,

The concept of personalized medicine is not new: The practice of medicine has always been about treating each individual patient, and clinicians have long observed that different patients respond differently to medical interventions. What is new is that paradigmatic developments in science and technology offer new promise for developing targeted therapeutics and tools for predicting who will respond to a medical therapy or who will suffer ill effects. (4)

The paradigm of personalized medicine can be illustrated as follows:

through Genomics and Personalized Medicine Act.(6,7)

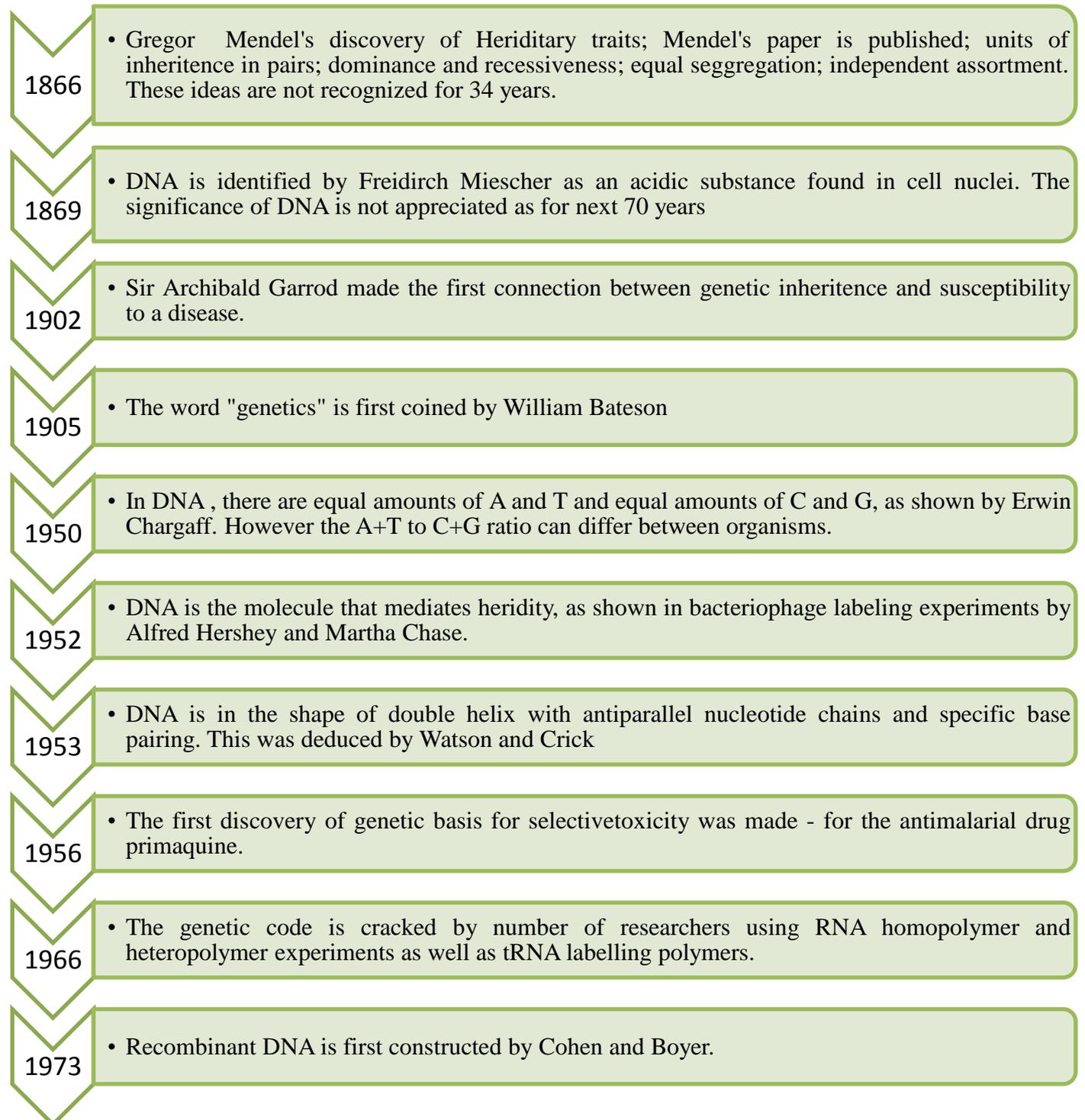
## BACKGROUND OF PERSONALIZED MEDICINE

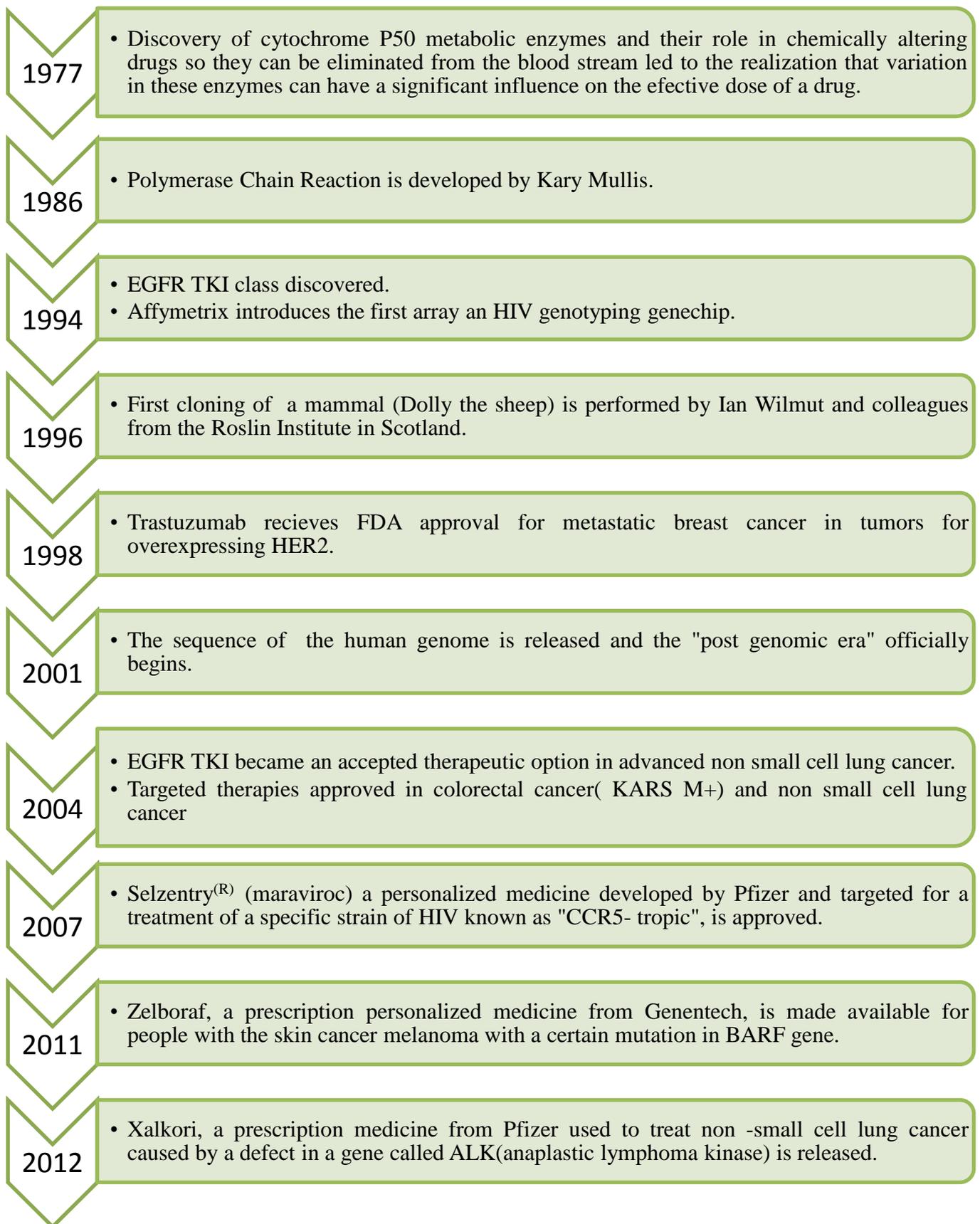
Disease diagnosis is often based on symptoms that might be indicative of several diseases. It is, however, now possible for the diagnosis of some diseases to be made more easily and in a more timely manner as genetic tests for disease-specific mutations become increasingly available.

Genome studies are revealing a large number of molecular biomarkers relating to specific gene variations. These may confirm the clinical diagnosis in the presence of overt disease. They may also indicate an asymptomatic person's susceptibility to a specific disease and/or more reliably predict a person's differential response to treatment. Such biomarkers can serve as the basis of new genomics-based predictive and diagnostic tests, the results of which may be used by a trained health professional to:

- diagnose a disease (and possibly the subtype) in an individual;

- assess an individual's risk of disease;
- identify whether an individual will benefit from particular interventions; and/or
- tailor dosing regimens to individual variations in metabolic response. (1)





**Figure 2: Timeline**

Personalized medicine is the application of genetic information to predict disease development, influence decisions about lifestyle choices, and tailor preventative interventions or medical treatment to the individual needs of each patient. Personalized medicine can allow screening, early intervention and treatment to be concentrated on those who will benefit, reducing expense and side effects for those who are not likely to benefit. It is important to note that the application of personalized medicine goes beyond genetic disease, and can optimize treatment for many diseases including HIV and epilepsy.

Through personalized medicine, it is anticipated that in time, the 'single-fit-all' drug will be replaced by more effective drug interventions and treatments that are specifically designed and customized to an individual's personal genetic profile.

**Genetic Variation:** It can be described as **single gene** or **complex**

- i) **Single gene** refers to a variation in a single gene that is sufficient to alter the phenotype (a mutation). However, not all sequence variations in single genes are causally linked; sometimes variants of unknown clinical utility are found and cannot be used in clinical decision making.
- ii) **Complex interactions** involve mutations in many genes, often with small cumulative effects, and interaction with environmental factors. With complex interactions, the nature and contribution of each of the implicated genes and the environment is not yet well understood.

**Genetic testing:** Genetic testing can be differentiated into somatic and germ cell genetics, based on the type of DNA mutations involved and their effect on disease. **Somatic cell** genetics refers to mutations acquired in the DNA of somatic cells some time after conception and are therefore not heritable. **Germ cell** genetics refers to mutations in the DNA of the germ cells (ova or sperm) and so are heritable.

## BENEFITS OF PERSONALIZED MEDICINE (8, 9)

Advocates of personalized medicine stress its potential to:

- detect disease at an earlier stage, when it is easier to treat effectively.
- enable the selection of optimal therapy and reduce trial-and-error prescribing.
- reduce adverse drug reactions.
- increase patient compliance with therapy.
- improve the selection of targets for drug discovery.
- reduce the time, cost, and failure rate of clinical trials.
- revive drugs that failed clinical trials or were withdrawn from the market
- avoid withdrawal of marketed drugs.
- shift the emphasis in medicine from reaction to prevention.
- reduce the overall cost of healthcare.
- predict susceptibility to disease, improve disease detection, preempt disease progression.
- customize disease prevention strategies

## GENOMIC MEDICINE

Simply defined, genomic medicine is the use of information from genomes (from humans and other organisms) and their derivatives (RNA, proteins, and metabolites) to guide medical decision making. The prospect of examining a person's entire genome (or at least a large fraction of it) to make individualized risk predictions and treatment decisions is now possible. Many patterns of gene expression across the entire genome are also now readily assayed. Thus, health and disease states can now be characterized by their molecular fingerprints to develop meaningful stratifiers for patient populations and to elucidate mechanistic pathways based on genome-wide data (10)

## PHARMACOGENETICS: ITS ROLE & EFFECTIVENESS

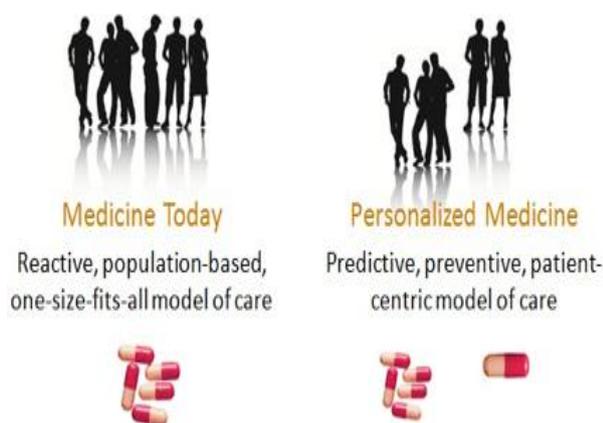
Pharmacogenetics describes the science that explores how genetic differences can lead to differences in the way certain medicines interact with the human body. These interactions can affect both the effectiveness of the medication and any side effects.(11)

The term **pharmacogenomics**, which often is used interchangeably with pharmacogenetics, refers to the application of genomic technologies to the study of pharmacogenetics.

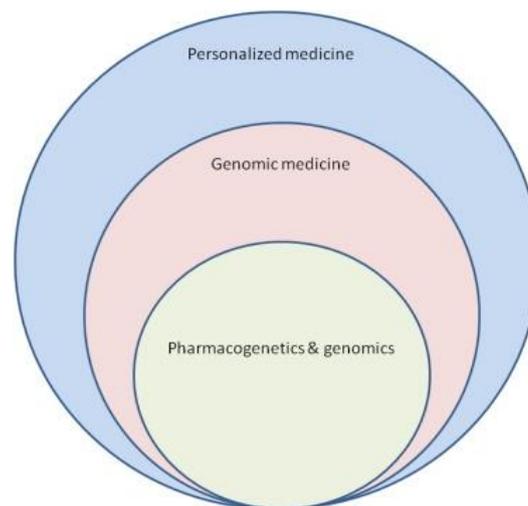
A patient's response to a drug is often linked to common genetic variations present in their genes. One type of genetic variation is the single nucleotide polymorphisms (SNPs). Knowing the types of SNPs/ genetic variations present in a patient can help predict the associated drug response. This can not only help physicians individualize drug therapy, it will also help improve effectiveness of the drug, decrease the

chance of negative side effects and save healthcare costs.(12)

Accurate prediction about drug response is crucial for individualized treatment. This is best made by combining an individual's genetic data with clinical findings and classifying individuals into subpopulations that differ in their response to a specific drug.(13) Using this approach, health care providers may be better equipped to move beyond the "one-size-fits-all" treatment strategy that defined much of patient care in the past, to care that is appropriate for unique patient subgroups.



**Figure 3 : Patient-centric model of care in personalized medicine**  
[www.cpmc1.coriell.org/personalized-medicine](http://www.cpmc1.coriell.org/personalized-medicine)



**Figure 4: Nested Relationship between Personalized Medicine, Genomic Medicine, and Pharmacogenetics and Genomics**

Applying pharmacogenetics ensures patients are prescribed the most effective drug or optimal dosage from the beginning of treatment. Pharmacogenetics can be used to minimise the likelihood of an adverse reaction to a medicine.(13)

For example, the drug Abacavir is approved in Australia for the treatment of patients with HIV. However, approximately 5% of patients suffer a potentially fatal hypersensitive reaction to this medication. Research has found that with a particular variation of a gene people with a gene called HLA-B are more likely to develop a reaction to Abacavir. Clinicians are advised to consider testing patients for the presence of this gene variant before they prescribe Abacavir.(14)

### FACTORS CAUSING VARIABILITY IN DRUG RESPONSES (15)

- 1) Genetic Factors: Mutation in genes for drug- metabolizing enzymes, drug transporters and targets.
- 2) Environmental Factors:
  - Chemicals
  - Coadministered drugs
  - Diet
  - Tobacco
  - Smoking & Alcohol use.
- 3) Physiological Factors: Age, sex & disease status.

## ROLE OF PERSONALIZED MEDICINE

The impact of Personalized Medicine, in six different areas are summarized which cover the

main activities of medical R&D and clinical practice. In many pre-clinical and clinical development steps Personalized Medicine methods will be applied. (16,17)

**Table 1:** The Role of Personalized Medicine

<p><b>In Basic Research</b></p>	<ul style="list-style-type: none"> <li>Personalized Medicine is involved in identifying biochemical pathways and related biomarkers that identify the genetic variations in diseases, help diagnose and target candidate pathways for particular therapeutic interventions.</li> <li>Personalized Medicine also considers drug metabolism and response to new therapeutic interventions.</li> </ul>
<p><b>In Drug Discovery and Development</b></p>	<ul style="list-style-type: none"> <li>Personalized Medicine provides a more mechanistic approach, using predictive information, for developing safer and more effective drug therapies for treating particular sub-population groups.</li> <li>Personalized Medicine is being used to predict how new drugs will work in cells</li> </ul>
<p><b>In Pre Clinical Testing</b></p>	<ul style="list-style-type: none"> <li>Personalized Medicine offers an approach to pre-clinical testing that can pro-actively inform drug development paths. Through a concept known as Phase 0 trials, small or micro-level dosages will be given to individuals to study the biology or pharmacology of the potential drug candidate, as is done in Phase I trials. With advanced tools, such as microscopy or imaging, pre-clinical testing will be undertaken to identify which drug candidate has the most favourable receptor binding or kinetics or metabolism or even proof-of-mechanism studies.</li> </ul>
<p><b>In Clinical Research</b></p>	<ul style="list-style-type: none"> <li>Personalized Medicine can be used to select participants based on their genetic predispositions to respond to certain types of therapies, resulting in more efficient, safer, less costly, and more rapid clinical studies.</li> <li>A new approach to “adaptive clinical trials” is being advanced, where patient outcomes from early phases of the trial are used to adjust the trial’s allotment of future patients in subsequent stages.</li> <li>Personalized Medicine offers an avenue for rescuing or reintroducing drugs that were found ineffective during previous clinical trials or had adverse drug reactions with a particular sub-group.</li> </ul>
<p><b>In Clinical Adoption</b></p>	<ul style="list-style-type: none"> <li>Personalized Medicine will offer physicians a more targeted drug therapy approach for treating their patients, particularly through the use of combination diagnostic-drug treatments.</li> <li>Advances in diagnostic technologies and the ability to demonstrate clinical utility will be key for moving Personalized Medicine forward.</li> </ul>
<p><b>In Health Care</b></p>	<p>Personalized Medicine offers a powerful new approach for improving public health:</p> <ul style="list-style-type: none"> <li>Identify individuals with predisposition for the development of a specific disease</li> <li>Early detection of a disease, resulting in improved outcome of treatment</li> <li>Predict the disease course</li> <li>Identify patients who are most likely to benefit from a particular drug</li> <li>Identify patients likely to be at increased risk for adverse drug reactions</li> <li>Monitor response to treatment for the purpose of adjusting treatment</li> <li>Addressing cost-effectiveness of drug treatments</li> </ul>

## THE PERSONALIZED MEDICINE LANDSCAPE

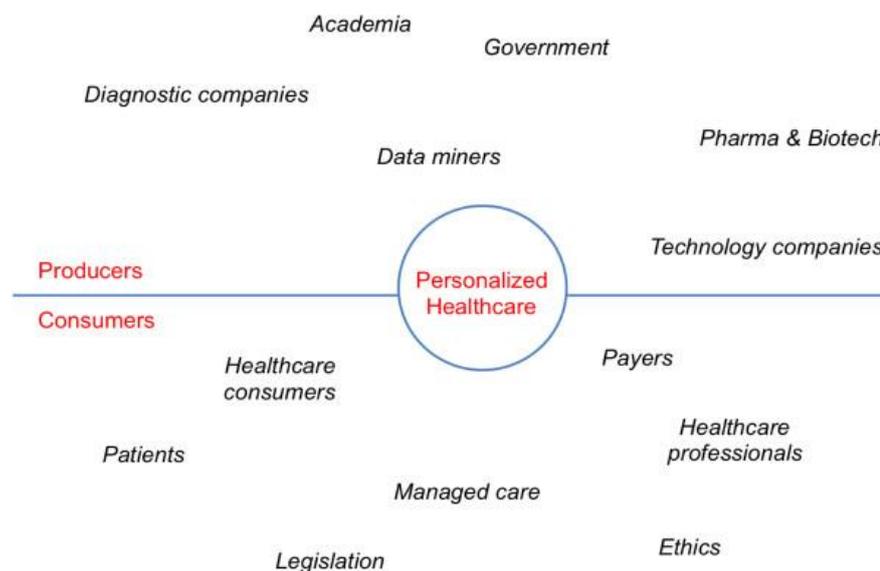
### The people and groups engaged in personalized medicine and helping to drive it forward.

The realization of personalized medicine relies on the input and contributions of a broad

community of stakeholders, all working together toward a shared goal of harnessing breakthroughs in science and technology to improve patient care. (18,19)

In the future, a patient will be surrounded by a huge amount of data points that uniquely define the individual medical history and will reflect the current health status.(20)

<p><b>Patients and consumers</b></p> <ul style="list-style-type: none"> <li>Participating in genetic testing and clinical trials and working with health care providers to proactively manage disease risk and/or treatment strategies</li> </ul>	<p><b>Health Care providers</b></p> <ul style="list-style-type: none"> <li>Moving from general to specific treatments, and from disease treatment to prevention</li> <li>Employing an understanding of the patient's genetic profile and utilizing new technologies to individualize the approach to disease prevention, detection, diagnosis, treatment, and management</li> </ul>
<p><b>Biopharmaceutical Companies:</b></p> <ul style="list-style-type: none"> <li>Developing targeted therapies and conducting innovative research based upon an understanding of genetic variation and its effects on the safety and effectiveness of the candidate drug</li> </ul>	<p><b>Diagnostic Companies:</b></p> <ul style="list-style-type: none"> <li>Developing and validating new diagnostics to enable personalized medicine.</li> <li>Developing tools and tests to analyze and interpret genetic information, improving the understanding of disease at the molecular level and a patient's likelihood to respond to drug therapy</li> </ul>
<p><b>Academic Researchers:</b></p> <ul style="list-style-type: none"> <li>Conducting basic and clinical research to uncover new insights into human genetics and the molecular basis of disease, enabling greater precision in diagnosis and more targeted drug development.</li> </ul>	<p><b>IT/Informatics Company:</b></p> <ul style="list-style-type: none"> <li>Creating electronic tools and resources to collect and store patient health information, making it available to inform clinical decisions and improve safety while protecting patient privacy</li> </ul>
<p><b>Advocacy Groups:</b></p> <ul style="list-style-type: none"> <li>Advancing personalized medicine in patient care by educating consumers and providers, accelerating research, and supporting necessary changes in policy and regulation.</li> </ul>	<p><b>Payers:</b></p> <ul style="list-style-type: none"> <li>Exploring new business models to incentivize the practice of personalized medicine through appropriate reimbursement of molecular diagnostics, targeted therapies, and other personalized treatment protocols</li> </ul>



**Figure: 5 Key Players involved in Personalized Medicine Health care System**

## CLINICAL APPLICATIONS OF PERSONALIZED MEDICINE

Personalized medicine can provide medical practitioners with an additional biological basis with which to categorize some diseases. This will influence genomic based improvements in screening, diagnosis and prognosis. It will also allow for greater optimization of preventative and therapeutic care.

Personalized medicine can facilitate disease prediction, prevention and treatment strategies by:

- determining if someone is at increased risk of developing a disease, followed by promotion of and support for compliance with available prevention strategies;
- diagnosing disease in development stage using optimal surveillance, thereby allowing more effective interventions or treatment options;
- enhancing therapeutic efficacy by ensuring the most appropriate drug is used and that the dosing regimen takes into consideration any genetic variants, which may influence metabolism of the drug; and

- avoiding preventable drug related complications and side effects resulting from generic “one size fits all” drug prescribing.

Medical practitioners will be able to provide more tailored prevention and treatment programs for their patients resulting in improved patient outcomes, reduced adverse events, and more cost effective use of health care resources.(21,22)

## Classification of Personalized Medicine

The use of personalized medicine is categorized into predictive medicine and treatment optimization, as outlined below.

### Predictive medicine

Genetic information can provide a more accurate prediction of the risk of developing a disease, disease progression, and severity of symptoms, in an individual. This information can be used to tailor prevention and treatment to that individual as well as to make informed choices relating to lifestyle, reproductive matters, screening and preventative treatments. A summary of the clinical utility of predictive medicine for some diseases is included in Table 2.

**Table 2:** Clinical Utility of Predictive Medicine.(22)

Disease	What the test detects	Reason for testing	Comments	Clinical utility
<b>Somatic cell genetics – single genes</b>				
Acute leukaemia	Minimal residual disease	Patients often relapse after an apparent cure	Has become standard care for acute promyelocytic leukaemia, chronic myeloid leukaemia and Philadelphia chromosome (Ph <sup>+</sup> ) positive acute lymphoblastic leukaemia	(*)Allows for a more accurate prognosis and to identify further treatment needs
<b>Germ cell genetics – single genes</b>				
Lynch Syndrome	Mutations in the MLH1, MSH2, MSH6, and PMS2 genes	Mutations in these genes increase the risk of developing Lynch syndrome; penetrance is not 100%	In families with Lynch Syndrome, MLH1 and MSH2 account for approximately 90% of detected mutations, MSH6 for approximately 7%-10% and PMS2 for fewer than 5%.	(*)Detection of mutations allows for surveillance which includes colonoscopy with removal of precancerous polyps every one to two years starting at age 25.
Huntington disease (HD)	Presence of HD mutation	Mutation confers 100% penetrance and HD is presently incurable	Though presently incurable, preventative therapies are being investigated. HD testing can relieve anxiety for unaffected individuals, and allow affected individuals to make informed life choices	(#)Allows for planning for life and long term health decisions, including family planning. May in future allow for protective.

Germ cell genetics – complex diseases				
Alzheimer disease	Type E4 of ApoE gene.	Identifying an increased risk allows early intervention and planning.	The testing has been used at population level to detect population level risk. The test is not accurate enough to predict individual risk	(^) Most cases occur sporadically and do not involve these mutations.

Notes:

(\*)Used in clinical practice but not formally evaluated

(#) Clinically useful (^) Limited clinical utility

### Treatment optimization

Many adverse drug reactions are the result of individuals being prescribed the incorrect dosage of medication. In addition to well understood variables such as age, sex, weight and body fat, genetic differences can give rise to differing responses to a given drug. This is because many enzymes involved in drug

response have genetic variants that may be associated with an increase or decrease in drug metabolism.(22)

Treatment optimization refers to pharmacogenetics/pharmacogenomics. Pharmacogenomics aims to match the best available drug or dose to an individual's genomic profile.

**Table: 3** Clinical Utility of Treatment Optimization (22)

Disease and Drug Test	Drug/test Purpose	Reason for Testing	Clinical Utility
<b>Somatic Cell Genetics</b>			
Breast cancer Herceptin® (trastuzumab)	Herceptin® is used to treat tumours which overexpress the HER2 protein. HER2 positive breast cancers can be targeted more effectively	Herceptin has significant side effects and in tumours not over-expressing in HER2 the risks outweigh the potential benefits	(^) Herceptin®, a costly drug can now be targeted to those most likely to respond and so as well as cost savings, it reduces the risks of complications in those unlikely to respond to it.
<b>Somatic Cell Genetics- Complex Interactions (Pharmacogenomic Type Test)</b>			
Breast cancer MammaPrint®	Measures the expression profile of 70 genes implicated in endocrine responsive breast cancer. Stratifies patients into high and low risk groups for relapse and metastasis	This can inform treatment decisions as high risk groups may need further chemotherapy treatment while low risk groups may only require hormone therapy and monitoring.	(**) Clinical utility is to be confirmed. Clinical use may be justified while ongoing studies confirm the role of MammaPrint® in clinical practice. This would assist in decision making particularly for treated early stage breast cancer when it is difficult to predict what type (if any) adjuvant therapy is needed
<b>Germ Cell Genetics- Single Genes:</b>			

Inflammatory bowel disease, transplantation, some forms of leukaemia Thiopurines	The thiopurine methyltransferase (TMPT) gene is important in the metabolism of thiopurines.	Some subtypes rapidly metabolise thiopurines (requiring higher doses) while others metabolise slowly (more likely to develop side effects).	(**)The ability to personalize dosages can reduce the risk of complications, while ensuring effectiveness. This is likely to be clinically useful.
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Notes:

(^) Clinically Useful

(\*\*) Under Evaluation

### **PUBLIC POLICY ISSUES IMPACTING PERSONALIZED MEDICINES**

Several clusters of significant public policy issues mark the pathway to the growth and acceptance of personalized medicine. A new healthcare paradigm with far-reaching

implications, personalized medicine requires us to examine our current approaches to clinical trials, intellectual property rights, reimbursement policies, patient privacy and confidentiality. Some of the issues raised by personalized medicine include (23-25):

1	<b>Intellectual Property</b>	A strong intellectual property system is necessary to stimulate investment in innovation. It is essential that government patent systems offer protection for innovations relating to personalized medicine, as well as high quality patent examination that allows patents of appropriate scope and quality.
2	<b>Regulatory Oversight</b>	The development of personalized medicine may require that regulatory bodies adopt some new approaches to product approval. This will entail new guidance about the processes for obtaining approval to commercialize new therapeutics, including when and under what circumstances the use of a new drug must be preceded and/or accompanied by the use of a diagnostic or screening test. These clinical trial rules will influence the drug, biotechnology, diagnostic and device industries.
3	<b>Reimbursement</b>	If the healthcare system is to secure the full benefits of personalized medicine, it must provide full and fair reimbursement for new technologies, products and services, based on market principles to the extent possible. The reimbursement system — both governmental and private payers — must have coverage and payment policies that support the timely adoption of new personalized medicine technologies, including both diagnostics and therapeutics.
4	<b>Privacy, Confidentiality and Patient's rights</b>	Patient protection is clearly a critical issue, and one that must be addressed to build public confidence — without which it will be impossible to collect the molecular and clinical data that is the foundation of personalized medicine capability. Among the issues that must be addressed: the implications of being identified as predisposed to a certain condition or non responsive to available treatments; the rights of non-consenting family members of the tested individuals; the implications for existing ethnic groups or as-yet-undefined genetic subgroups; and the psychological and social effects of genetic testing for the individual tested.

### **Other Ethical and Policy Issues Relevant To Personalized Medicine (26)**

- 1 Fairness in access to genomic technologies
- 2 Patient education

3 Provider Education  
 4 Healthcare System Infrastructure  
 5 R& D incentives for industry  
 6 What to do if no alternatives are available  
 7 Consequences of not performing a test if available  
 8 Fairness in the use of genomic information by insurers, employers, courts, schools, adoption agencies and the military, etc.

9 Psychological impact, stigmatization due to misunderstanding about pharmacogenomics information.  
 10 Uncertainties and misunderstanding regarding gene tests.

### REGULATORY POLICY AND GUIDANCE DOCUMENTS FROM FDA (27)

Following regulatory policies and guidance documents are issued by Food and Drug Administration:

2005	:	Guidance on PG Data Submissions Concept Paper on Drug-Diagnostic Co-Development.
2007	:	Guidance on Pharmacogenomic Tests and Genetic Tests for Heritable Markers.
2008	:	E15 Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories.
2010	:	Guidance on Qualification Process for Drug Development Tools
2011	:	E16 Guidance on Biomarkers Related to Drug or Biotechnology Product Development: Context, Structure, and Format of Qualification Submissions. Guidance on in vitro Companion Diagnostic Devices.
2012	:	Guidance on Clinical PG: Premarketing Evaluation in Early Phase Clinical Studies. Guidance on Clinical Trial Designs Employing Enrichment Designs.
2013	:	Guidance on Clinical Pharmacogenomics: Pre-market Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling.
In process	:	Guidance on Drug-Diagnostic Co-development.

### LEGISLATIVE POLICIES INVOLVED IN PERSONALIZED MEDICINE

#### 1) The Health Insurance portability and Accountability Act

The Health Insurance Portability and Accountability Act of 1996 (HIPAA ) was enacted to ensure that personal medical information stored, accessed, or processed adheres to a set of privacy guidelines.<sup>(28)</sup> These security rules outline measures to adequately safeguard all electronic Protected Health Information (PHI). However, the rules only applied to federally funded institutions, and gaps remained in privacy protections with respect to employers and insurance providers.<sup>(29)</sup>

#### 2) The Genetic Information Non-Discrimination Act (29-30)

The GINA of 2005 would explicitly prohibit employers and health insurers from discriminating against individuals on the

basis of their genetic risk factors, thus filling certain gaps in HIPAA privacy protections.

Signed into law May 21, 2008, by President George W. Bush, GINA overcame key barriers to moving PM forward. Thanks to GINA, genetic information cannot form the basis of health insurance underwriting decisions, and employers cannot use it to make hiring, firing, and promotion selections. Forbidding health insurers and employers from using genetic information means that privacy concerns about health information technology (HIT) also dwindle, as do similar concerns about biobanks. The passage of GINA was important to stakeholders in research too. The possibility of genetic discrimination hindered progress in PM by hobbling basic research into the genetic aspects of disease:

- There had been concern that employers and health insurers would have access to the results of genetic tests; this could keep people from asking their physicians

for those tests, resulting in an inability to predict and prevent diseases.

- It was feared that genetic information obtained from participation in research studies would fall into the hands of employers and health insurers; this could deter people from enrolling in genetic research studies.

### 3) The Affordable Care Act (29)

The ACA of 2010 establishes guaranteed issue, meaning that issuers offering insurance in either the group or individual market must provide coverage for all individuals who request it. The law prohibits issuers of health insurance from discriminating against patients with genetic diseases by refusing coverage because of “pre-existing conditions.” ACA offers additional protections for patients with genetic diseases by establishing that certain health insurance issuers may only vary premiums based on a few specified factors, such as age or geographic area, thereby prohibiting the adjustment of premiums because of medical conditions.

### 4) The American With Disabilities Act (28,29)

The Americans with Disabilities Act (ADA) prohibits discrimination in employment, public services, accommodations, and communications based on a disability. In 1995, the Equal Employment Opportunity Commission (EEOC) issued an interpretation suggesting that discrimination based on genetic information relating to illness, disease, or other disorders is prohibited by the ADA. Although laws on genetic privacy are evolving to meet the needs of patients, current laws can make it harder to collect and analyze aggregated clinical data for the development of new personalized treatments and diagnostics. The expectation to protect privacy and the need to encourage research must be properly balanced so that medical care can continue to improve.

## GOVERNMENT AGENCIES SHAPING PERSONALIZED MEDICINE (31)

Four organizations in the U.S. and Europe will play a key role in shaping the future of Personalized medicine.

### Centers for Medicare & Medicaid Services (CMS)

As the largest healthcare payer in the U.S, CMS could have a profound impact on the advancement of targeted diagnostics and therapeutics and the adoption of a proactive healthcare model that emphasizes health, wellness and the prevention of disease. Reimbursement models developed by CMS tend to be adopted by most private insurers. CMS is expected to move forward in the direction of adopting a more outcomes based reimbursement model that could spur the development of targeted diagnostics and Therapeutics.

### Food and Drug Administration (FDA)

As the federal agency responsible for approval and regulation of drugs and diagnostics, the FDA faces a major challenge to develop a clear, viable pathway for the approval of new targeted diagnostics, therapeutics, and theranostics. Efforts such as the Critical Path Initiative are paving the way for collaborations with industry to address the challenge and accelerate progress in personalized medicine. The FDA also could speed progress by supporting conditional approvals—allowing smaller and less expensive clinical trials for personalized medicines, then utilizing personal mobile devices (smart phones) to monitor patient compliance and performance to determine if problems are emerging, thereby enabling quality and safety.

### National Institutes of Health (NIH)

The NIH, which is responsible for U.S. medical research in the public domain, is guided by its NIH Roadmap for Medical Research, which includes funding for research into systems biology, genomics and proteomics, and other aspects of personalized medicine. Bolstered by \$10 billion in funding from the economic stimulus, the NIH can enhance its research into biomarkers of disease and the development of targeted diagnostics and therapeutics. The NIH also is creating an integrated network of leading AMCs through its Clinical and Translational Science Awards (CTSA) program. These

institutions will likely be at the forefront of scientific research to advance the science of personalized medicine.

### European Medicines Agency (EMA)

The European Medicines Agency (EMA) is the governing body of the European Union that is responsible for promoting public health and safety and has regulatory approval and oversight of new diagnostics and therapeutics. It is roughly equivalent to the FDA in the United States but is a decentralized organization. EMA could accelerate the spread of personalized medicine through its approval process, under which only a single application is required to secure approval of a drug or diagnostic in all EU countries. One major objective of the EMA is to make safe and effective medicines available to patients. Better medicines need to reach the market in a timely manner and be evaluated using state-of-the-art methods. A key goal of the EMA Road Map 2010 is to foster research and innovation in the pharmaceutical industry across the European Union. To this end, an “EMA/CHMP think-tank group on innovative drug development” was created. The group comprises EMA staff and several members of different scientific committees/ working parties of the Agency acting as an internal focus group. These experts aim to identify scientific bottlenecks to the development of innovative medicines, both in the industry’s R&D and in the academic environment. (20)

### CONCLUSION

The long arc of medical history has been one in which diagnostic capability has evolved from the metaphysical, to the anatomical, to the cellular, and ultimately to the molecular level. Now that diseases can be sub-classified using evidence well beyond what is visibly obvious into categories that presage the course of disease and its likely response to treatment, there is an obligation to act on that information.

Personalized medicine offers a new paradigm for the development of drugs and the practice of medicine. While the potential benefits of personalized medicine include development of drugs that are safer and more effective for specific disease populations, such benefits cannot be realized until certain obstacles to

adoption are removed. Obstacles in public policy include uncertain regulatory requirements, insufficient insurance reimbursement for diagnostic tests linked to pre-emptive care, incomplete legal protections to prevent genetic discrimination, the lack of a comprehensive healthcare information technology system, and a medical education system that has not taught physicians how to incorporate personalized medicine diagnostics or pharmacogenomics into their practices. Understanding all of these key factors – from obstacles to incentives – is a necessary step in determining how to apply resources to influence the direction of personalized medicine and its progress.

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### CONFLICT OF INTEREST

Author declares that there are no conflicts of interest.

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