International Journal of Science and Research (IJSR)
ISSN: 2319-7064
Impact Factor 2025: 7.089

Genomic Medicine and Personalised Treatment: From Sequence to Clinical Decision: Applications, Barriers and Future Directions

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Abstract: ***Genomic medicine is an interdisciplinary field that combines genomics with bioinformatics to give healthcare professionals both the conceptual tools and the practical methods needed to personalise diagnosis and treatment on the basis of an individual patient's genetic information. Advances in DNA sequencing, proteomics and computational biology have made it possible to select therapies for the person rather than for the average patient, to treat rare inherited disorders that were previously undiagnosable, and to edit the genome directly using technologies such as CRISPR/Cas. This paper reviews the scientific foundations of the field, traces the path from a biological sample to a clinical decision, and examines the four domains in which genomic medicine has had the greatest effect: oncology, cardiovascular disease, rare inherited disorders and pharmacogenomics. It sets out the evidence provided by landmark clinical trials, and analyses the technical, economic, ethical and legal obstacles that continue to limit routine adoption. The central finding is that the scientific case for genomic medicine is now largely settled, while the implementation case is not. Sequencing has become fast and inexpensive; interpretation, integration with electronic health records, workforce training, equitable access and the governance of highly sensitive personal data have not kept pace. Genomic medicine will change how disease is diagnosed and treated, but the speed of that change will be determined by health systems and policy rather than by the technology itself.***

Keywords: genomic medicine, genomics, personalised treatment, precision medicine, next-generation sequencing, pharmacogenomics, CRISPR, bioinformatics, cardiology, oncology

1. Introduction

Genomic medicine is healthcare that uses genomics and bioinformatics in the diagnosis and treatment of disease. Its foundation was laid by the Human Genome Project, which established how genetic information influences health and identified the variations that can be used to improve treatment. The landmark studies that made this possible include the determination of the double-helix structure of DNA by Watson and Crick, the development of chain-termination sequencing by Sanger, the introduction of shotgun sequencing, and the emergence of next-generation and third-generation sequencing platforms.

Recent advances allow DNA to be sequenced faster, more reliably and far more cheaply, with greater accuracy and longer read lengths than were possible even a decade ago. Together with progress in computational biology and proteomics, this permits treatment to be individualised in order to maximise effectiveness and minimise harm. The purpose of this paper is to analyse the role of genomic medicine in personalised healthcare, to examine its benefits and its limitations, and to identify the challenges that must be addressed by future research and by health policy.

The distinction between genetics and genomics is worth stating at the outset, because the two are frequently confused. Genetics is the study of individual genes and their inheritance, and it explains conditions caused by a single defective gene. Genomics is the study of the entire genome, including the interaction of many genes with one another and with the environment, and it is what allows common and complex conditions such as cancer, diabetes and cardiovascular disease to be approached at the molecular level. Personalised or precision medicine is the clinical application of that knowledge: the selection of the right intervention, at the right dose, for the right patient.

2. Genetic and Genomic Principles

2.1 DNA, genes and genomes

DNA, genes and genomes define the genetic makeup of an organism. DNA is a double-helix molecule capable of adopting several secondary structures, while the genome is the sum of all the DNA in the body, including both the coding genes and the far larger quantity of non-coding sequence that regulates them. Despite the obvious diversity between individuals, the genome of any two people is highly similar, and it is the small proportion of variable sequence that accounts for differences in appearance, in susceptibility to disease and in response to medication.

Two properties of the genome matter for everything that follows. The first is that it is essentially fixed: apart from somatic mutation, the sequence read at any age is the sequence a person will carry for life, so a single test retains its value for decades in a way that a blood pressure reading or a blood count does not. The second is that it is shared: a pathogenic variant identified in one patient is present, on average, in half of that patient's first-degree relatives. A genomic result is therefore never entirely private to the individual tested, and this is what makes both cascade screening so efficient and the ethics of disclosure so difficult.

2.2 Genetic variation

The term genetic variation refers to genetic differences that occur both within and between individuals. Variation may take the form of single-nucleotide polymorphisms, in which one base is exchanged for another, or of structural changes such as copy-number variants and insertions and deletions. All of these contribute to phenotypic diversity by regulating the normal function of genes, and all can affect both a person's response to medication and their risk of developing particular diseases. Table 1 summarises the principal categories.

Table 1: Principal categories of genetic variation and their clinical significance

Type of variation	Description	Clinical relevance
Single-nucleotide polymorphism (SNP)	Substitution of a single base at a defined position in the genome	Drug metabolism, common disease susceptibility
Insertion or deletion (INDEL)	Addition or loss of a small number of bases	Frameshift mutations in inherited disease
Copy-number variant (CNV)	Duplication or loss of a larger segment of DNA	Developmental disorders, tumour gene amplification
Structural variant	Inversion, translocation or complex rearrangement	Gene fusions driving certain cancers
Epigenetic modification	Chemical change such as methylation that alters expression without changing sequence	Tumour suppressor silencing, environmental response

Genome-wide studies have shifted the focus of the field from monogenic disorders, in which a single gene explains the condition, towards complex diseases such as cancer and cardiovascular disease, in which many variants each contribute a small effect. This shift is central to personalised genomic medicine, because it makes it possible to identify biomarkers for conditions that no single gene can explain.

3. Sequencing Technologies and the Genomic Toolkit

The history of the field is best understood through its technology, summarised in Figure 1. Each step reduced either the cost or the time required to read a genome, and each opened a set of clinical questions that had previously been unanswerable.

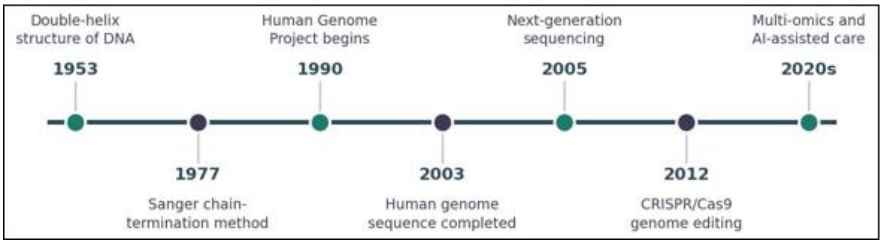

Figure 1: Milestones in the development of genomics and its translation into clinical practice

Next-generation sequencing plays a decisive role in modern genomics by allowing rapid sequencing at a relatively low price. Its arrival changed the economics of the field more than any other single development, as Figure 2 illustrates: sequencing a human genome cost tens of millions of dollars at the completion of the Human Genome Project and now costs a few hundred. The consequence is that the expensive step in genomic medicine is no longer generating the data, but interpreting it and acting upon it.

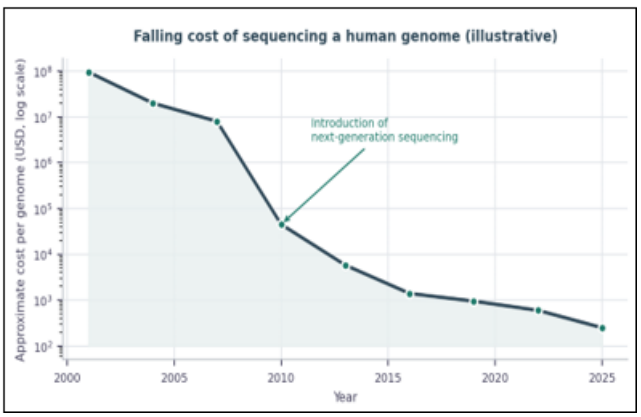

Figure 2: The decline in the cost of sequencing a human genome. The steep fall after 2007 reflects the introduction of next-generation platforms

A range of genetic tests is now available, and choosing correctly between them is itself a clinical skill. Single-gene tests, gene panels, whole-exome sequencing, whole-genome sequencing and chromosomal analysis each answer a different question at a different cost, as set out in Table 2. Combining copy-number variation analysis with single-nucleotide variant analysis yields more reliable detection of genetic abnormality, particularly during pregnancy. Fluorescence in situ hybridisation is used to identify tumour-associated abnormalities that guide the diagnosis and treatment of cancer. Genomic tests also allow the prediction of prostate cancer and the individualised management of patients with blood cancers, while whole-exome and whole-genome sequencing permit the diagnosis of severe epilepsies such as Dravet syndrome, pyridoxine-dependent epilepsy and glucose transporter 1 deficiency, each of which has a different and specific treatment.

Table 2: Principal genomic tests, their scope and their common indications

Test	What it examines	Typical clinical indication
Single-gene test	One gene known to cause a specific condition	Confirming a clinically suspected diagnosis
Gene panel	A defined group of genes associated with one phenotype	Inherited cardiomyopathy, hereditary cancer risk
Whole-exome sequencing (WES)	All protein-coding regions, about 1-2% of the genome	Undiagnosed disease with a likely coding cause
Whole-genome sequencing (WGS)	Coding and non-coding sequence across the genome	Complex or unresolved presentations; research
Chromosomal microarray	Copy-number changes across all chromosomes	Developmental delay, congenital anomaly
Fluorescence in situ hybridisation (FISH)	Specific chromosomal regions within cells	Tumour classification and companion diagnostics

4. From Genome to Clinical Decision

Sequencing a genome is only the first step of a longer pipeline, shown in Figure 3. A sample is collected under informed consent and sequenced; raw reads are aligned to a reference genome and variants are called and filtered; each remaining variant is then classified according to its likely effect. This interpretation stage is where the real difficulty lies. A typical genome differs from the reference at millions of positions, the overwhelming majority of which are harmless, and the task is to identify the handful that explain the patient's presentation.

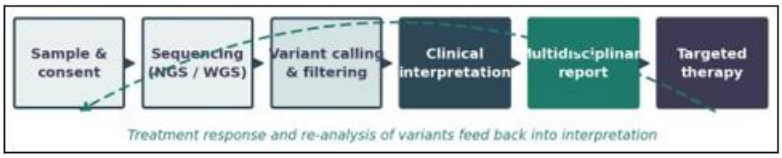

Figure 3: The pipeline from biological sample to targeted therapy, including the feedback of treatment response into variant interpretation.

Variants are usually reported on a five-point scale running from benign to pathogenic, with a middle category of variants of uncertain significance. That middle category is clinically awkward: it represents a finding that can neither be acted upon nor safely dismissed, and it is more common in patients from populations that are under-represented in reference databases. Because classification improves as databases grow, periodic re-analysis of stored data can convert an uncertain result into a diagnosis without any new sequencing, which is one of the strongest arguments for retaining genomic data securely over time.

The final steps are clinical. A multidisciplinary team, typically including a clinician, a clinical geneticist, a bioinformatician and a genetic counsellor, agrees a report; the report informs treatment; and the observed response feeds back into the interpretation of the same variants in future patients. Genomic medicine is therefore cyclical rather than linear, and its accuracy improves with use.

One further point deserves emphasis. A genomic result is probabilistic rather than deterministic for most common conditions: it shifts an estimate of risk rather than declaring an outcome. Communicating that distinction to patients is a clinical skill in its own right, and failure to do so produces either false reassurance or unnecessary alarm. Genetic counselling is therefore not an optional adjunct to genomic medicine but part of the test itself, and the shortage of trained counsellors is one of the practical limits on how quickly services can expand.

5. Clinical Applications

5.1 Oncology

Progress in genomic medicine over the last decade has improved the diagnosis and treatment of cancer through the identification of gene amplifications, deletions, mutations and fusion events by genomic profiling. Widely used profiling assays act simultaneously as companion diagnostics, determining not only what the tumour is but which drug it should receive.

Targeted therapy and immunotherapy have transformed treatment, producing dramatic responses in specific disease settings: HER2-positive breast cancer treated with trastuzumab, non-small-cell lung cancer carrying an EGFR mutation treated with osimertinib, advanced melanoma treated with ipilimumab, giant cell tumour of bone treated with denosumab, and Merkel cell, urothelial and renal cell carcinomas that respond to avelumab. Genomic testing of tumour tissue from previously treated patients with lung adenocarcinoma has identified compound EGFR mutations that responded to osimertinib with partial remission. These successes are summarised in Table 3.

Table 3: Representative genomic findings and the targeted therapies they direct.

Genomic finding	Targeted agent	Disease setting
HER2 amplification	Trastuzumab	HER2-positive breast cancer
EGFR activating mutation	Osimertinib	Non-small-cell lung cancer
High tumour mutational burden	Pembrolizumab	Melanoma and other solid tumours
CTLA-4 pathway	Ipilimumab	Advanced melanoma
RANK ligand expression	Denosumab	Giant cell tumour of bone
PD-L1 pathway	Avelumab	Merkel cell, urothelial and renal cell carcinoma

The picture is not uniformly favourable. Targeted therapy can cause secondary cancers and therapy-related malignancies, including melanoma in patients with triple-negative breast cancer treated with pembrolizumab and T-cell lymphoma following CAR T-cell therapy. Resistance also develops,

often through a second mutation in the same pathway, which is why serial rather than single genomic testing is increasingly the standard of care. Research into the tumour microenvironment, including the possibility that targeting extracellular matrix stiffness could slow tumour progression, indicates that the genome of the tumour alone does not determine its behaviour.

5.2 Cardiovascular disease and gene therapy

Cardiovascular medicine benefits from genomics in two distinct ways. The first is diagnostic: genetic testing identifies pathogenic variants underlying cardiomyopathies, inherited arrhythmias such as long QT syndrome, and familial hypercholesterolaemia. Because these conditions are inherited in a predictable pattern, a single confirmed diagnosis allows cascade testing of relatives, so that preventive treatment can begin in people who are still entirely well. Familial hypercholesterolaemia is the clearest example: it is common, seriously under-diagnosed, and highly treatable once identified.

The second contribution is therapeutic. Adeno-associated viral vectors, CRISPR/Cas genome editing and ultrasound-mediated targeted microbubble delivery all offer routes to promoting tissue repair and regeneration in the heart. These approaches remain largely experimental, and the practical obstacles are considerable: delivering an editing system efficiently to cardiac tissue, restricting its activity to the intended sequence, and demonstrating durable benefit over years rather than months.

5.3 Rare inherited disorders

Rare disease is where genomic medicine has changed clinical practice most decisively. Individually uncommon, these conditions are collectively frequent, and affected families have historically endured a diagnostic odyssey lasting years. Next-generation sequencing frequently resolves such cases in a single test. Significant progress has been made in the diagnosis and treatment of cystic fibrosis, mitochondrial disease, spinal muscular atrophy, haemophilia, Fanconi anaemia and primary immunodeficiency.

Treatment has followed diagnosis. Adeno-associated viral vectors, lentiviral vectors, stem-cell therapy and targeted drug treatment have all reached the clinic for spinal muscular atrophy, and gene editing using CRISPR/Cas is expected to provide durable treatment for sickle cell disease and thalassaemia. A diagnosis is valuable even where no treatment exists: it ends uncertainty, allows accurate genetic counselling and reproductive choice, prevents further unnecessary investigation, and connects families to others with the same condition.

5.4 Pharmacogenomics

Pharmacogenomics applies genomic biomarkers to predict drug response and toxicity, enabling treatment to be personalised before the first dose rather than adjusted after an adverse reaction. Genetic markers strongly influence how an individual responds to a medicine, although disease state, diet and concurrent drugs also contribute. Genome-wide association studies, regulator-recognised pharmacogenomic biomarkers and the genotype-informed prescribing guidance developed by the Clinical Pharmacogenetics Implementation Consortium have together made this the most clinically mature part of the field.

Variants in CYP2C19 substantially affect the response to P2Y12 inhibitors, and genotype-guided dosing of clopidogrel and prasugrel is now recommended. Carriers of the loss-of-function alleles CYP2C19*2 or CYP2C19*3 have reduced enzyme activity, giving a weaker antiplatelet effect and higher cardiovascular risk, whereas the CYP2C19*17 allele increases enzyme activity, improving efficacy but raising bleeding risk. Other genes, including ABCB1 and CES1, also influence the response but are not routinely genotyped. Polymorphisms in UGT1A4 and UGT2B7 and in the transporters OCT1 and ABCG2 affect the metabolism and disposition of lamotrigine and contribute to the wide variation between individuals, so that dose adjustment is often required. In oncology, a patient found to be a CYP2D6 intermediate metaboliser was switched from tamoxifen to anastrozole in accordance with consortium guidance, because tamoxifen requires CYP2D6 activity to be converted into its active form.

Table 4: Selected gene-drug pairs with established clinical guidance.

Gene	Affected drug	Clinical consequence of variation
CYP2C19	Clopidogrel, prasugrel	Loss-of-function alleles reduce antiplatelet effect; *17 raises bleeding risk
CYP2D6	Tamoxifen, codeine, antidepressants	Poor metabolisers fail to activate the prodrug; alternative agent required
UGT1A4, UGT2B7	Lamotrigine	Altered clearance and inter-individual variability; dose adjustment needed
TPMT, NUDT15	Azathioprine, mercaptopurine	Reduced activity causes severe myelosuppression at standard doses
HLA-B*15:02	Carbamazepine	Markedly increased risk of severe cutaneous adverse reaction

5.5 Prenatal and reproductive genomics

Non-invasive prenatal testing analyses cell-free fetal DNA circulating in maternal blood and has substantially reduced the number of invasive procedures carried out for the detection of common chromosomal aneuploidies. Carrier screening before conception identifies couples at risk of transmitting a recessive condition, and preimplantation genetic testing allows embryos to be assessed before transfer. Each of these applications is technically mature and each raises questions that technology cannot answer, concerning the conditions for which testing should be offered, the counselling that must accompany it, and the risk that routine offer becomes tacit expectation. The clinical requirement here is not better sequencing but better consent and counselling.

5.6 Pathogen and microbial genomics

Sequencing is applied to the genome of the pathogen as readily as to that of the patient. Rapid sequencing of bacterial isolates identifies resistance determinants far faster than culture-based sensitivity testing, allowing antibiotic therapy

to be narrowed early; genomic comparison of isolates distinguishes a true outbreak from unrelated cases in the same ward; and sequencing of viral genomes tracks the emergence of variants across populations. This is the part of genomic medicine with the widest public-health reach, because a single sequencing facility can serve an entire region, and it is also the part in which turnaround time matters most.

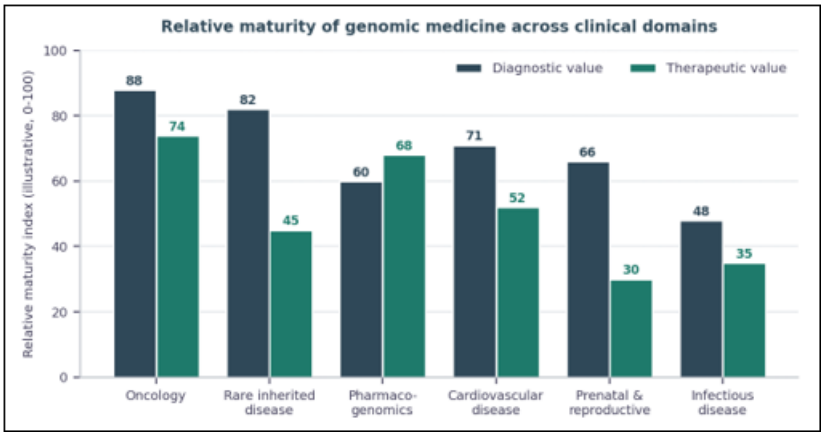

Figure 4: Relative maturity of genomic medicine across the main clinical domains, distinguishing diagnostic from therapeutic value

6. Evidence from Clinical Trials

Personalised medicine uses genomic and molecular biomarkers to select the most appropriate therapy for an individual at the right time, and its clinical value has been demonstrated repeatedly. The MINDACT trial showed that a seventy-gene expression profile supports sound decisions about adjuvant chemotherapy in early-stage breast cancer, allowing a substantial proportion of women at high clinical risk but low genomic risk to avoid chemotherapy safely. The PROMISE study indicated that high-sensitivity troponin and interleukin-6 serve as biomarkers for the prognosis of coronary artery disease, including non-obstructive disease that conventional imaging can miss.

In oncology, genome-wide analysis has shown that patients whose lung adenocarcinoma carries STK11/LKB1 mutations alongside mutant KRAS respond poorly to anti-PD-1 immunotherapy, which allows a different treatment to be chosen at the outset rather than after months of ineffective therapy. A further study found that KRAS G12 mutations may indicate resistance to trifluridine and tipiracil in metastatic colorectal cancer. Outside oncology, a personalised approach benefited frail older adults with sarcopenia, for whom individualised blood-pressure targets reduced cardiovascular risk, and magnesium supplementation has been reported to reduce TMPRSS2 DNA methylation, suggesting a route to personalised prevention. These results share a common structure: a biomarker separates patients who will benefit from those who will not, and treatment is allocated accordingly.

What these trials establish collectively is that biomarker-guided allocation of treatment can be tested with the same rigour as a drug. The design is now well understood: patients are stratified by a marker, treatment is randomised within strata, and the question asked is not whether the drug works but whether the marker correctly identifies who it works for. Trials of this kind are harder to recruit for, because each stratum requires its own adequate sample, and this is one reason that evidence in genomic medicine accumulates more slowly in less common conditions than the underlying science would suggest.

7. Challenges in Implementation

Despite these advances, genomic medicine faces obstacles that are organisational and economic as much as scientific. Figure 5 shows the barriers most frequently reported by institutions attempting to introduce genomic services.

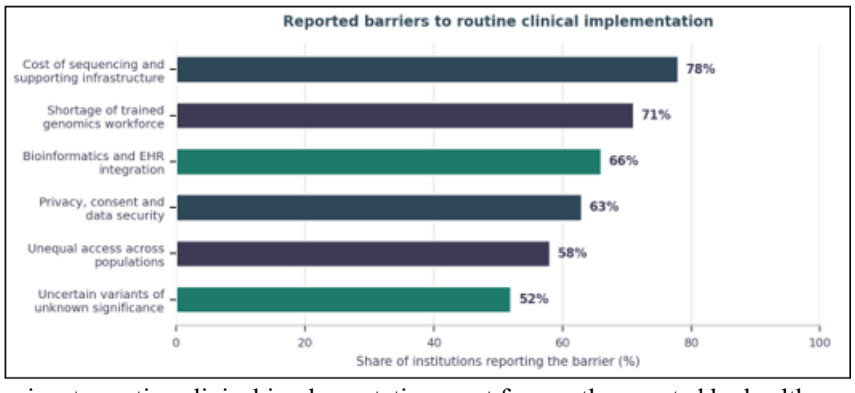

Figure 5: Barriers to routine clinical implementation most frequently reported by healthcare institutions.

- **Technical and logistical demands.** Clinical genomics requires bioinformatics infrastructure for sequencing and analysis, and the integration of results into the electronic health record in a form clinicians can act upon. It also requires health professionals educated in genomics, since a report that cannot be interpreted has no clinical value.
- **Cost and access.** Although sequencing costs have fallen sharply, the surrounding technologies, storage and analytical capacity remain expensive. Establishing genomic services is capital-intensive and requires sustained investment, policy support and integration into national health systems.
- **Variants of uncertain significance.** A large proportion of findings cannot yet be classified as benign or pathogenic, and the proportion is higher for under-represented populations, which risks widening rather than narrowing health inequity.
- **Privacy and data security.** Genomic data is uniquely identifying, is shared with biological relatives who never consented, and cannot be reissued if compromised, which places demands on encryption, access control and audit far beyond those of ordinary medical records.
- **Ethical concerns.** Informed consent, incidental findings, the psychological burden of risk information and the possibility of genetic discrimination all require careful handling and clear institutional policy.
- **Unequal access.** Minority populations, women, rural residents and those who are uninsured or on low incomes are less likely to receive genetic testing, cancer screening or targeted therapy, producing measurable disparities in outcome.

8. Privacy, Ethics and Equity

The storage and regulation of genomic data raise questions of both security and law. Genetic data is sensitive and personal, and frameworks such as the Health Insurance Portability and Accountability Act restrict access to authorised healthcare providers, although the level of protection varies between jurisdictions. Genomic data should be encrypted in storage, in transmission and in use, and strict audit controls are required because access typically involves many stakeholders. The reason for this care is straightforward: exposure of genetic information can lead to genetic discrimination and social stigmatisation, and legal, technical and ethical safeguards are all necessary to prevent it.

Genetic discrimination is the unfair treatment of an individual on the basis of their DNA, and it may take the form of denied employment or refused insurance. The Genetic Information Nondiscrimination Act of 2008 makes it unlawful for health insurers or employers to use genetic information in determining eligibility, but it does not extend to life, disability or long-term care insurance, where protection depends on individual state legislation. Table 5 summarises the principal instruments and their limits.

Table 5: Legal and institutional safeguards for genomic information, and their principal gaps.

Instrument	Protection provided	Principal limitation
HIPAA	Restricts disclosure of identifiable health information	Does not prevent lawful secondary use by covered entities
GINA (2008)	Prohibits use of genetic data in health insurance and employment	Excludes life, disability and long-term care insurance
Affordable Care Act	Prevents exclusion for pre-existing conditions	Does not extend to non-health insurance products
Institutional review	Requires informed consent for research use of samples	Consent obtained once may not cover future re-analysis

Improving equity requires more than legal protection. It requires more diverse representation of minority and vulnerable groups in genomic research, because reference databases built largely from populations of European ancestry produce more uncertain results for everyone else. It also requires that testing be available in community hospitals and primary care rather than only in academic centres, alongside investment in workforce education and infrastructure, partnership between healthcare providers and the communities they serve, and public education about genetic rights so that people understand how their information is used. Strengthening anti-discrimination law and extending it to insurance products currently outside its scope would reduce the risk of discrimination further and build the trust on which participation depends.

9. Future Directions

Sequencing itself continues to develop. Short-read sequencing is inexpensive and highly accurate over reads of roughly one hundred to three hundred bases, but struggles with repetitive regions; long-read sequencing is more costly and less accurate per base yet resolves complex structural variation that short reads cannot see. Combining the two approaches yields more complete and more accurate results than either alone, and the combination is becoming standard in difficult cases.

Bioinformatics is the second frontier. The growth of pharmacogenomics and the accumulation of genomic, clinical, expression and imaging datasets require secure cloud storage in which accessibility and privacy are both preserved. Artificial intelligence applied to these datasets can identify biomarkers and patterns that improve diagnosis, prognosis and treatment selection, with early results in oncology, cardiology and neurodevelopmental disorders, but its use demands the same ethical discipline as any other handling of patient data.

The widest development is multi-omics: the integration of genome, transcriptome, proteome, epigenome, metabolome, radiome and microbiome data into a single picture of the patient. Genomics alone captures potential rather than state, describing what a cell might do rather than what it is doing; combining data types addresses that limitation and reveals disease-specific molecular markers and therapeutic targets. Applied across cancer, inflammatory bowel disease, diabetes and many other conditions, this approach classifies patients by their biology rather than by their symptoms, and it is likely to be the mechanism through which precision medicine

extends from rare disease and cancer into everyday clinical care.

Finally, the economics of the field will change as the balance of cost shifts from generating data to interpreting and storing it. As sequencing approaches the cost of a routine laboratory test, the argument for sequencing once and re-analysing many times becomes compelling: a genome generated for one clinical question can answer later questions without a new sample, provided the data is stored securely and the consent under which it was collected anticipates that use. Designing consent, storage and re-contact policies that make this possible is an administrative task rather than a scientific one, and it is likely to determine how much value health systems extract from the data they already hold.

10. Conclusion

The development of genomic medicine has deepened the understanding of genetic variation and, through advances in DNA sequencing, multi-omics and the incorporation of genetic information into clinical practice, has improved both diagnosis and individualised treatment. Genomic testing now identifies the cause of inherited disease, directs targeted therapy in cancer, guides preventive treatment in cardiovascular medicine and predicts drug response before the first prescription is written. The accuracy of diagnosis has increased, conditions that were previously overlooked are now identified, and treatment can be selected for effectiveness and safety in the individual patient.

The limitations are equally clear. Much remains unknown about the significance of individual variants, the ethical questions raised by genetic information are unresolved, and access is unequal. It is therefore essential to continue developing the field: to make it accessible across populations, to address ethical concerns openly, and to improve the bioinformatics on which interpretation depends. The scientific foundation of genomic medicine is secure. What determines its future is whether health systems can build the infrastructure, the workforce and the public trust required to use it, and it is on that question, rather than on any remaining technical obstacle, that the delivery of appropriate and high-quality individualised treatment now depends.

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