



Understanding the Genetic Basis of Human Diseases

Dr. Elena Vargas

Department of Molecular Genetics, University of Barcelona, Spain

Email: elena.vargas@ub.edu

Abstract: *The exploration of the genetic basis of human diseases has revolutionized modern medicine by offering insights into the molecular underpinnings of health and illness. Genetic variations, whether inherited or acquired, contribute to the susceptibility, onset, and progression of various disorders. This article reviews the categories of genetic diseases, the role of genetic and genomic technologies in diagnosis, and the translational potential of precision medicine. It also addresses ethical challenges and future directions in genetic research, with emphasis on integrating genome-wide data into clinical practice to improve patient outcomes.*

Keywords: *Genetic disorders, Genome sequencing, Inherited diseases, Precision medicine, Human genome*

INTRODUCTION:

Understanding the genetic foundation of human diseases has become a cornerstone of biomedical research. The human genome comprises more than 3 billion base pairs, and even minor mutations can result in significant phenotypic consequences. While some disorders are monogenic—caused by mutations in a single gene—others are polygenic, involving complex interactions between multiple genes and environmental factors. Advances in sequencing technologies have enabled researchers to uncover pathogenic variants, trace inheritance patterns, and tailor interventions to individual genetic profiles. This growing body of knowledge not only enhances diagnostic accuracy but also fuels the development of targeted therapies.

1. Classification of Genetic Disorders:

The genetic basis of human diseases is diverse and complex, broadly classified into **monogenic**, **polygenic**, **chromosomal**, and **mitochondrial** disorders. These categories reflect the origin, molecular nature, and inheritance of the genetic alterations that lead to disease.

Monogenic Disorders:

Monogenic or single-gene disorders are caused by mutations in a single gene. These mutations may involve substitutions, insertions, deletions, or duplications that affect the gene's ability to produce a functional

protein. These disorders often follow **Mendelian inheritance patterns**, meaning they can be inherited as **autosomal dominant**, **autosomal recessive**, or **X-linked traits**.

A well-known example is **Cystic Fibrosis (CF)**, which is inherited in an autosomal recessive manner. Mutations in the CFTR gene lead to defective chloride channel function in epithelial cells, resulting in the accumulation of thick mucus in the lungs, pancreas, and other organs. This causes chronic respiratory infections, pancreatic insufficiency, and male infertility. Because the defect lies in a single gene, targeted genetic testing can provide definitive diagnosis and enable carrier screening in families.

Other examples of monogenic disorders include **sickle cell anemia** (HBB gene), **Huntington's disease** (HTT gene), and **Marfan syndrome** (FBN1 gene). Advances in gene therapy and CRISPR-Cas9 gene editing are beginning to offer new hope for the treatment of such conditions.

Polygenic Disorders:

Polygenic or complex disorders result from the interaction of **multiple genes**, often coupled with **environmental and lifestyle factors**. Each genetic variant may contribute only a small effect individually, but collectively they can significantly influence disease risk. Unlike monogenic disorders, polygenic diseases do not follow clear inheritance patterns, making their prediction and diagnosis more challenging.

Schizophrenia, for example, is a severe mental illness characterized by delusions, hallucinations, and cognitive impairment. It is influenced by hundreds of small genetic variations—such as those in COMT, DISC1, and other neurodevelopmental genes—and also by environmental risk factors like prenatal stress, drug use, and urban upbringing. The **polygenic risk score (PRS)** is a modern approach used to assess an individual's inherited risk by aggregating the effects of multiple variants across the genome.

Other common polygenic disorders include **type 2 diabetes**, **hypertension**, **coronary artery disease**, and **asthma**. Since these diseases are widespread and impact global health significantly, large-scale population genomics projects and GWAS have been instrumental in identifying risk loci and developing preventive strategies.

Chromosomal Disorders:

Chromosomal disorders involve **large-scale genetic abnormalities**—either in the **number** or **structure** of chromosomes. Numerical abnormalities, such as **trisomy** (an extra chromosome) or **monosomy** (a missing chromosome), typically arise from errors in meiotic cell division (nondisjunction). Structural abnormalities may include translocations, deletions, duplications, or inversions of chromosomal segments.

Down syndrome (Trisomy 21) is one of the most common chromosomal disorders, occurring in approximately 1 in 700 live births. Individuals with this condition have three copies of chromosome 21, which disrupts normal development. The syndrome is characterized by intellectual disability, distinct facial features, hypotonia, and an increased risk of congenital heart disease and Alzheimer's-like dementia.

Other examples include **Turner syndrome** (monosomy X in females), **Klinefelter syndrome** (XXY in males), and **Cri-du-chat syndrome** (5p deletion). These disorders are usually diagnosed via **karyotyping**, **fluorescence in situ hybridization (FISH)**, or **comparative genomic hybridization (CGH)**.

Mitochondrial Disorders:

Unlike nuclear DNA, **mitochondrial DNA (mtDNA)** is inherited **exclusively from the mother** and exists in multiple copies per cell. Mutations in mtDNA can lead to defects in **oxidative phosphorylation**, the process that generates cellular energy (ATP). Because of the high energy demands of tissues like the brain, muscles, and heart, mitochondrial disorders often present with **multisystem symptoms**.

MELAS syndrome (Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes) is a classical mitochondrial disorder. It usually begins in childhood or adolescence with symptoms like recurrent headaches, seizures, lactic acidosis, and stroke-like episodes that can lead to temporary paralysis or vision

loss. It is commonly associated with the **A3243G mutation** in the MT-TL1 gene of the mitochondrial genome.

Diagnosing mitochondrial disorders requires a combination of **clinical evaluation, muscle biopsy, lactate testing, and mitochondrial genome sequencing**. The variable expression and heteroplasmy (coexistence of mutated and normal mtDNA) complicate both diagnosis and treatment.

These four major categories represent the diverse molecular origins of genetic diseases. Accurate classification is essential for understanding pathogenesis, guiding diagnostic workflows, and selecting appropriate therapeutic strategies. As genetic research advances, particularly through next-generation sequencing and systems biology, clinicians are now better equipped to classify, predict, and treat these diseases in a personalized manner.

2.Role of Genomic Technologies in Diagnosis:

The emergence of **genomic technologies** has catalyzed a paradigm shift in biomedical diagnostics, moving from symptom-based classification to **molecular-level precision diagnostics**. Technologies such as **Next-Generation Sequencing (NGS)** and **Whole-Exome Sequencing (WES)** have provided clinicians and researchers with tools that can decode the genetic blueprint of an individual at an unprecedented scale, speed, and resolution, thereby uncovering the underlying molecular etiology of numerous human diseases.

Next-Generation Sequencing (NGS):

NGS encompasses a suite of advanced sequencing methods that allow **parallel sequencing** of millions of DNA fragments. It significantly differs from traditional **Sanger sequencing** in that it does not rely on the sequential processing of a single DNA strand, but rather on massively parallel reactions that can read **entire genomes or targeted regions** within a few hours or days. This scalability makes NGS applicable to a wide variety of diagnostic scenarios, ranging from single-gene testing to **whole-genome sequencing (WGS)**. In a clinical setting, NGS enables the simultaneous examination of multiple genes associated with similar phenotypes, enhancing the probability of reaching a correct diagnosis in a **cost-effective** and **timely** manner.

NGS is used in multiple diagnostic applications, including **oncology (tumor profiling)**, **neurology (genetic epilepsy panels)**, **cardiology (inherited arrhythmias)**, and **infectious diseases (pathogen identification and resistance mutation detection)**. For example, in cancer genomics, **targeted NGS panels** can reveal actionable mutations in genes like KRAS, BRAF, or ALK, directly influencing treatment decisions and patient prognosis. In infectious disease diagnostics, NGS can identify pathogens and their resistance profiles, even when cultures fail or in polymicrobial infections.

Whole-Exome Sequencing (WES):

A major subset of NGS, **WES** specifically targets **all protein-coding regions (exons)** of the genome. Although exons make up only ~1–2% of the genome, they harbor the majority of known pathogenic mutations responsible for Mendelian and other heritable diseases. WES is thus a strategic compromise between comprehensiveness and cost, offering high diagnostic yield for genetic disorders at a fraction of the cost and complexity of WGS.

Clinical utility of WES has been particularly well demonstrated in rare diseases and undiagnosed conditions. For example, in cases of intellectual disability or unexplained metabolic syndromes, WES has helped identify mutations in novel genes not previously associated with any disease. Trio-based WES (proband and parents) is especially effective in detecting **de novo mutations** or **compound heterozygous variants**, common in sporadic and autosomal recessive diseases. The diagnostic yield of WES varies by clinical indication but is generally reported to be **25–50%**, much higher than traditional diagnostic approaches.

In addition to identifying **pathogenic single-nucleotide variants (SNVs)** and **small insertions or deletions (indels)**, advanced computational tools can also infer **copy number variations (CNVs)** and **splicing defects** from WES data, enhancing its diagnostic scope. Variant interpretation is guided by criteria from the **American College of Medical Genetics and Genomics (ACMG)**, with variants classified as pathogenic, likely pathogenic, variants of uncertain significance (VUS), likely benign, or benign.

Identification of Pathogenic Variants and Risk Alleles:

A major objective of using NGS and WES in diagnosis is to pinpoint **pathogenic variants**—mutations that directly cause disease by disrupting gene function. These can include nonsense mutations, missense mutations that alter amino acid sequence, frame-shift mutations, and mutations affecting splicing. Once identified, such mutations can be used for **genetic counseling, carrier screening, prenatal diagnosis, and treatment planning**.

NGS also aids in the detection of **risk alleles**, which do not directly cause disease but increase the likelihood of developing it. These are particularly important in **polygenic diseases** like diabetes, schizophrenia, and cardiovascular disorders. Combining these alleles into **polygenic risk scores (PRS)** allows for risk stratification at the population level, enabling early intervention or lifestyle modification.

For instance, in **breast cancer**, women with high PRS and pathogenic variants in BRCA1/2 can be monitored more closely or offered prophylactic treatment. In cardiogenetics, identification of mutations in genes like MYH7 or TNNT2 enables early diagnosis of hypertrophic cardiomyopathy, potentially preventing sudden cardiac death.

Advantages, Challenges, and Future Directions:

The advantages of NGS and WES include:

High throughput and ability to sequence multiple genes simultaneously

Precision in identifying rare or novel mutations

Scalability from individual gene panels to full genome analysis

Cost-effectiveness, particularly in comparison to sequential testing of single genes

However, challenges remain:

Data interpretation is complex, especially for VUS

Ethical concerns about incidental findings (e.g., unrelated pathogenic variants)

Data privacy and storage, as genomic data is sensitive and voluminous

Access and equity, particularly in low-resource settings

The future lies in **integrating AI and machine learning** for variant interpretation, **using deep phenotyping**, and expanding the use of **multi-omics approaches** (e.g., genomics, transcriptomics, proteomics) for a comprehensive understanding of disease mechanisms. Ultimately, the role of genomic technologies is moving from rare disease diagnosis to **mainstream clinical practice**, reshaping medicine into a more predictive, preventive, and personalized discipline.

3.Implications for Personalized and Precision Medicine:

Personalized medicine—often used interchangeably with **precision medicine**—represents a fundamental shift from the traditional "one-size-fits-all" model of healthcare toward a **genotype-driven, patient-specific approach**. This model seeks to leverage a person's genetic, environmental, and behavioral information to tailor disease prevention, diagnosis, prognosis, and treatment strategies. Two key pillars of this approach are **pharmacogenomics** and **predictive genetic testing**, both of which are pivotal in improving therapeutic efficacy and minimizing adverse effects.

Pharmacogenomics and Genotype-Guided Therapies:

Pharmacogenomics studies how an individual's **genetic variation** affects their **response to drugs**. Genes encoding drug-metabolizing enzymes, drug transporters, and drug targets often harbor polymorphisms that result in differences in drug absorption, metabolism, distribution, and excretion. These variations can transform a standard dose of medication into a toxic or ineffective treatment if not adjusted for genetic background.

For example:

CYP2C19 polymorphisms impact the activation of clopidogrel, a commonly prescribed antiplatelet drug. Patients with **CYP2C19** loss-of-function alleles have reduced drug activation and higher risk of cardiovascular events post-angioplasty.

VKORC1 and **CYP2C9** genotypes affect warfarin sensitivity and metabolism, respectively. Personalized warfarin dosing based on these genotypes significantly reduces the risk of bleeding or thrombosis.

Genotype-guided prescribing is not limited to cardiology. In **psychiatry**, variations in **CYP2D6** and **CYP2C19** affect the metabolism of antidepressants and antipsychotics. In **oncology**, testing for mutations in **BRAF** (e.g., in melanoma) or **ALK** (e.g., in lung cancer) determines the use of specific targeted therapies like vemurafenib or crizotinib. These examples underscore the rise of **therapeutic stratification**, where treatment is optimized not by trial-and-error, but through molecular diagnostics.

Predictive Genetic Testing and Disease Risk Estimation:

Predictive genetic testing involves analyzing an individual's DNA to determine **inherited susceptibility** to certain diseases, particularly those with a strong genetic basis. This is critical for **early intervention, lifestyle modification, and preventive strategies**. For instance:

BRCA1/BRCA2 mutation carriers have up to an 85% lifetime risk of breast cancer. Knowledge of these mutations can lead to more frequent screening, lifestyle changes, or even prophylactic mastectomy.

Lynch syndrome (hereditary nonpolyposis colorectal cancer) is associated with mutations in mismatch repair genes (**MLH1**, **MSH2**, etc.), and carriers are recommended for early and regular colonoscopy screening.

Furthermore, **polygenic risk scores (PRS)**, derived from genome-wide association studies (GWAS), quantify cumulative risk from multiple common variants for diseases like coronary artery disease, type 2 diabetes, and Alzheimer's. While individually these variants confer small effects, in aggregate, they help stratify individuals into low, medium, or high-risk categories.

Patient Stratification and Biomarker-Driven Care:

In precision medicine, **patient stratification** refers to the segmentation of patients into subgroups based on **molecular biomarkers, genomic signatures, or disease endotypes**. This stratification allows healthcare providers to make more **precise predictions about disease progression, response to treatment, and prognosis**.

For example:

In **non-small cell lung cancer (NSCLC)**, patients are stratified based on the presence of mutations in **EGFR**, **ALK**, or **ROS1**, which determines eligibility for targeted therapies like osimertinib or crizotinib.

In **rheumatoid arthritis**, stratification based on biomarkers like anti-CCP antibodies and **HLA-DRB1** alleles helps predict disease severity and guide biologic therapy selection.

In **pediatric leukemia**, patients are classified based on chromosomal translocations (e.g., **BCR-ABL1**), which direct the use of specific tyrosine kinase inhibitors.

Beyond treatment, patient stratification also enhances **clinical trial design**. By enrolling molecularly defined subpopulations, trials can achieve higher statistical power with fewer participants and demonstrate efficacy more clearly—thereby accelerating regulatory approval.

Challenges and Ethical Considerations:

Despite its transformative potential, personalized medicine poses several challenges:

Variant of Uncertain Significance (VUS): Not all detected genetic variations have a known clinical consequence, making interpretation complex.

Data privacy and consent: Genomic data is sensitive; there are concerns about how it is stored, shared, and used—especially by insurers or employers.

Equity and accessibility: The cost and availability of genomic testing may widen disparities in healthcare, especially in low- and middle-income countries.

Clinical implementation gap: Many healthcare systems lack infrastructure, trained personnel, and regulatory frameworks to integrate precision medicine at scale.

To address these issues, frameworks like the **Clinical Pharmacogenetics Implementation Consortium (CPIC)** and guidelines from the **FDA and EMA** are being developed to standardize the interpretation of pharmacogenomic tests and support clinical decision-making.

The role of genomic technologies in enabling **precision medicine** is reshaping the landscape of modern healthcare. By tailoring interventions to a patient's genetic profile, pharmacogenomics reduces trial-and-error prescribing, predictive testing allows for preemptive intervention, and stratification enables more accurate disease modeling and treatment allocation. While challenges in data interpretation, ethics, and infrastructure persist, the trajectory is clear: medicine is evolving toward an era where treatment is not only more effective but inherently **personalized**, improving outcomes while reducing costs and side effects.

4. Ethical, Legal, and Social Considerations:

As genomic technologies become increasingly integrated into clinical practice and public health, they raise profound **ethical, legal, and social implications (ELSI)** that extend far beyond scientific discovery. Central among these are concerns surrounding **genetic privacy, informed consent, and data sharing**, all of which are essential to maintaining public trust and safeguarding individual autonomy. Unlike other forms of health data, **genomic information is uniquely identifiable and predictive**, revealing not only personal health risks but also information about relatives, ancestry, and future generations. This makes **genetic privacy** particularly sensitive. The unauthorized access, use, or disclosure of such data could lead to stigmatization, psychological harm, or misuse by third parties such as employers or insurers. Even when data is anonymized, the richness of genomic datasets may allow for re-identification using computational techniques.

Informed consent in genetic testing must be robust, transparent, and dynamic. Unlike standard medical procedures, genetic testing can yield **unanticipated results**, such as incidental findings (e.g., discovering a BRCA1 mutation while testing for cardiovascular disease), **variants of uncertain significance**, or **familial risks**. Patients must be informed not only about the primary purpose of the test but also about the potential for such findings, their implications, and whether they wish to receive them. Moreover, **longitudinal consent** may be required, especially for biobank participation or when data is used for future research. The process must also account for differences in literacy, language, cultural norms, and understanding of genetic risk, ensuring truly **autonomous and informed decision-making**.

Data sharing plays a critical role in genomic medicine by enabling researchers to pool data from multiple sources to improve variant interpretation, discover new gene-disease associations, and refine polygenic risk scores. However, it poses ethical challenges. While data sharing accelerates scientific progress, it may compromise individual privacy if proper safeguards are not in place. Regulations such as the **General Data Protection Regulation (GDPR)** in the European Union and **HIPAA** in the United States govern how genetic data can be stored, transferred, and accessed. International collaborations must navigate the **ethical**

tension between the need for open science and the obligation to protect individual rights, particularly when genomic data is stored in cloud platforms or shared across borders.

One of the most contentious areas is the **implication of genetic information for insurance and employment**. There is a growing concern that individuals with certain genetic predispositions could face **genetic discrimination**—being denied health, life, or disability insurance, or being treated unfairly in the workplace. To address these risks, several countries have enacted legal protections. For instance, the **Genetic Information Nondiscrimination Act (GINA)** in the United States prohibits the use of genetic information by health insurers and employers. However, GINA does not extend to life insurance, disability insurance, or long-term care insurance, leaving significant **regulatory gaps**. In jurisdictions without such laws, the fear of discrimination may deter individuals from undergoing beneficial genetic testing, undermining public health efforts.

Equally complex are the **reproductive and familial implications** of genetic testing. Knowledge of heritable mutations (e.g., Huntington's disease, Tay-Sachs disease, or fragile X syndrome) can influence reproductive choices. Couples may seek **preimplantation genetic diagnosis (PGD)** during in vitro fertilization to avoid passing on serious conditions, raising ethical questions about embryo selection and the potential for eugenics. Moreover, the disclosure of genetic information can have unintended consequences within families, such as uncovering non-paternity or leading to **moral dilemmas about whether to share genetic risk with relatives** who may not wish to know. Professional guidelines increasingly emphasize “**duty to warn**” versus **respect for autonomy**, leaving clinicians in ethically ambiguous positions.

In conclusion, while genomics offers immense promise for personalized medicine, it must be guided by **carefully constructed ethical, legal, and social frameworks**. These should ensure that genetic advances are implemented with respect for privacy, equity, and justice, and that individuals retain control over how their genetic data is used. Continuous dialogue between scientists, ethicists, policymakers, and the public is essential to navigating the rapidly evolving terrain of genomic medicine with responsibility and foresight.

5.Future Directions in Genomic Medicine:

The future of **genomic medicine** is poised at the intersection of **biotechnology, data science, and personalized healthcare**, with transformative potential driven by emerging innovations such as **CRISPR-Cas9 gene editing** and **artificial intelligence (AI)-assisted genomic interpretation**. These tools are not only expanding the frontiers of diagnostic accuracy and therapeutic specificity but are also enabling a transition from reactive treatment to **proactive and predictive healthcare models**.

The advent of **CRISPR-Cas9** (Clustered Regularly Interspaced Short Palindromic Repeats) has revolutionized gene editing by providing a precise, programmable, and cost-effective tool for modifying DNA. Unlike older gene-editing techniques like zinc-finger nucleases or TALENs, CRISPR allows researchers to **target specific genomic loci** with unprecedented accuracy, enabling both gene knockouts and corrections. In **clinical applications**, CRISPR is being explored for treating monogenic disorders such as **sickle cell anemia, beta-thalassemia, and Leber congenital amaurosis**, with promising early-phase clinical trial results. For instance, ex vivo editing of hematopoietic stem cells to correct the HBB gene in sickle cell patients has demonstrated successful reintroduction and symptom resolution.

Furthermore, **in vivo gene editing**—where CRISPR components are delivered directly into the patient's body—is now being trialed for diseases like **transthyretin amyloidosis**, with encouraging outcomes and minimal off-target effects. Future developments aim to refine the CRISPR platform through enhancements like **base editing** and **prime editing**, which allow single nucleotide changes without double-strand breaks, reducing the risk of unintended mutations. Ethical and regulatory challenges, particularly around **germline**

editing, remain critical concerns. The global scientific community has largely agreed on a moratorium on human germline editing for reproductive purposes, emphasizing the need for strict oversight, public engagement, and ethical consensus.

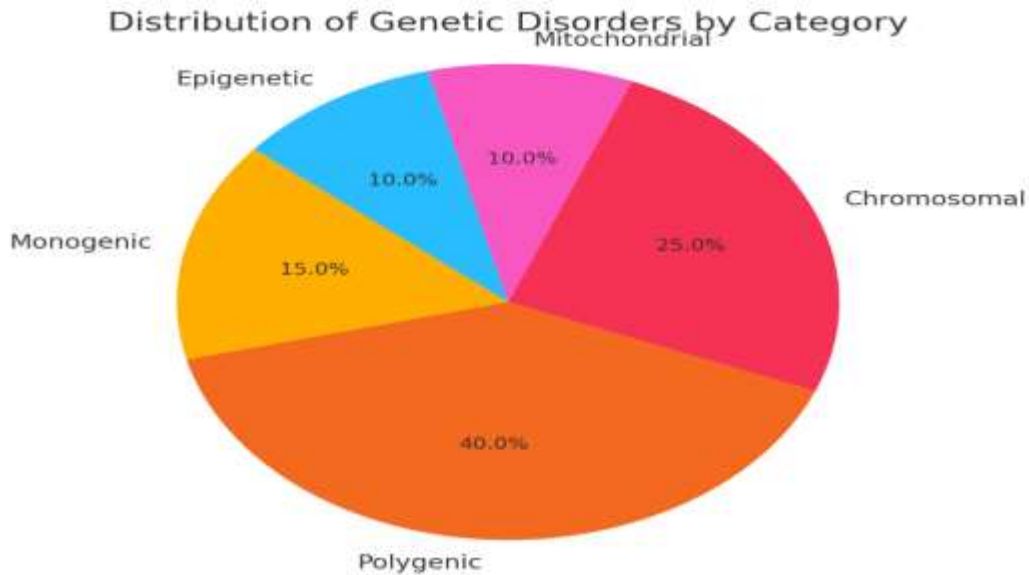
Parallel to gene editing, the explosion of **genomic data** has necessitated advanced tools for interpretation, leading to the integration of **artificial intelligence (AI) and machine learning (ML)** in genomic medicine. AI algorithms can analyze vast datasets generated from **whole-genome sequencing (WGS)**, **transcriptomics**, and **epigenomics** to identify **patterns, correlations, and clinically significant variants** that might be missed by human analysts. Tools like **DeepVariant**, developed by Google, use deep neural networks to accurately call genetic variants. Similarly, platforms such as **AlphaFold**, developed by DeepMind, predict protein folding and structural implications of mutations, enhancing our understanding of genotype-phenotype relationships.

AI is also driving improvements in **variant classification, phenotype prediction, and disease risk modeling**. For example, **natural language processing (NLP)** algorithms are used to mine literature and databases for functional annotation of variants, while **ensemble learning models** combine multiple data types—genomic, clinical, imaging—to stratify patients and predict disease trajectories. Importantly, AI models are being integrated into **clinical decision support systems**, enabling real-time analysis of patient genomes and assisting physicians in selecting personalized treatments or clinical trials.

In addition, the synergy of AI and CRISPR is being explored to **optimize guide RNA design, predict off-target effects, and model gene networks** to understand systemic effects of edits. This integration enhances both the safety and efficacy of genome editing, accelerating the path from bench to bedside. Furthermore, **multi-omics approaches**—combining genomics, proteomics, metabolomics, and microbiomics—are being powered by AI to develop comprehensive molecular portraits of patients, ultimately informing **precision diagnostics and targeted therapeutics**.

Looking ahead, genomic medicine is expected to evolve into a fully **data-driven, predictive discipline**, where early disease risk is assessed through polygenic scores, interventions are genetically optimized, and gene therapy becomes routine for a wide array of disorders. However, to realize this vision, **ethical, legal, and social considerations** must be addressed in parallel, ensuring transparency, equity, and public trust. Interdisciplinary collaboration between geneticists, bioinformaticians, ethicists, and clinicians will be essential to navigate the complexities of this genomic future.

Distribution of Genetic Disorders by Category



Summary:

The genetic basis of human diseases encompasses a diverse range of mechanisms, from single-gene mutations to complex polygenic interactions. The integration of high-throughput genomic tools has dramatically improved our understanding of pathophysiology and therapeutic responses. As precision medicine gains traction, clinicians can offer tailored interventions based on individual genetic profiles. However, ethical and policy frameworks must evolve in parallel to protect patients' rights and ensure equitable access. Future advances in genetic engineering and bioinformatics will likely redefine the diagnosis, treatment, and prevention of human diseases.

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