Chapter

Pharmacogenomics of "Core" Essential Medicines

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Abstract

Pharmacogenomics uses information about a person's genetic makeup to choose the drugs dosage regimens that are likely to work best for that particular person. The genomic research has changed the "one size fits all" approach and opened the door to more personalized approaches that consider individual genetic makeup tend to enhance the efficacy and safety of drugs; thus saving time and money. Patient DNA influences multiple steps in which the drugs interact with the body and where will the drug act in the body. Genetic makeup-based prescription, design, and implementation of therapy do not only improve the outcome of treatments, but also reduce the risk of toxicity and other adverse events. The aim of the chapter is to explore the documented pharmacogenomics of essential as per pharmacogenomic biomarkers in drug labeling; and suggest efficacy and safety modifications. Polymorphism of drug metabolizing enzymes has the greatest effect on inter individual variability of drug response; affecting the response of individuals to drugs used in the treatment of diseases. Also, genetic deficiency of some enzymes limits effectiveness of drugs in treating concerned diseases. Gene testing prior to initiating concerned treatment is the best clinical practice that to enhance the efficacy and safety of drugs.

Keywords: Pharmacogenomics, 21st WHO essential medicines "core" list, genetic testing

1. Introduction

The National Institute of General Medical Sciences define pharmacogenomics (or pharmacogenetics) as is a field of research that studies how a person's genes affect how he or she responds to medications [1]. The Centers for Disease Control (CDC) have regarded pharmacogenomics as an important example of precision medicine whereby medical treatment is tailored for each patient; based on individual genetic makeup [2]. The National Human Genome Research Institute further contended that Pharmacogenomics uses information about a person's genetic makeup (or genome) to choose the drugs and dosages that are likely to work best for that particular person. The field is an amalgam of two fields; namely pharmacology (the science of how drugs work) and genomics (the science of the human genome) [3].

The long term goal of pharmacogenomics is to help doctors select the drugs and dosage regimens best suited for each person. This is done in order to eliminate the ancient perspective that drugs have been developed with the idea that each drug works pretty much the same in everybody. But genomic research has changed that

"one size fits all" approach and opened the door to more personalized approaches to using and developing drugs [3]. The approaches that consider individual genetic makeup tend to enhance the efficacy and safety of drugs; thus saving time and money.

The World Health Organization (WHO) defines essential medicines as those medicines that satisfy the priority health care needs of the population and are selected with due regard to evidence on efficacy and safety, and comparative cost-effectiveness. Essential medicines are intended to be available within the context of a well-functioning healthcare system at all times in adequate quantities, in the appropriate dosage forms, with assured quality and adequate information, and at a cost the individual and the community can afford [4]. Since 1977, WHO developed a model Essential Medicines List (EML) that could be adapted by member states in order to keep essential medicines up to date in a healthcare system. The current version of the list is the 21st WHO EML updated in June 2019 [5].

With the background given above about pharmacogenomics and essential medicines, the aim of the chapter is to explore the documented pharmacogenomics of essential medicines "**core list**" of 21st WHO EML as per United States Food and Drug Administration (USFDA) Table of Pharmacogenomic Biomarkers in Drug Labeling updated in June 2020 [6]; and suggest therapeutic modifications that can be done in order to enhance efficacy and safety of essential medicines.

1.1 How pharmacogenomics work

Patient DNA influences multiple steps in which the drugs interact with the body and where will the drug act in the body.

1.1.1 Drug receptors

In order to interact with the body, most drugs associate with cellular molecules called receptors. The receptor is the component of a cell or organism that interacts with a drug and initiates the chain of events leading to the drug's observed effects [7]. The patient genetic makeup (DNA) determines the type of receptors to have and their quantities, which can affect the response to the drug. As illustrated in **Figure 1** below, some individuals might need a higher or lower amount of the drug than most people or a different drug.

A living example of this kind of a scenario is the case of Trastuzumab emtansine (T-DM1) and breast cancer tumors with or without human epidermal growth factor

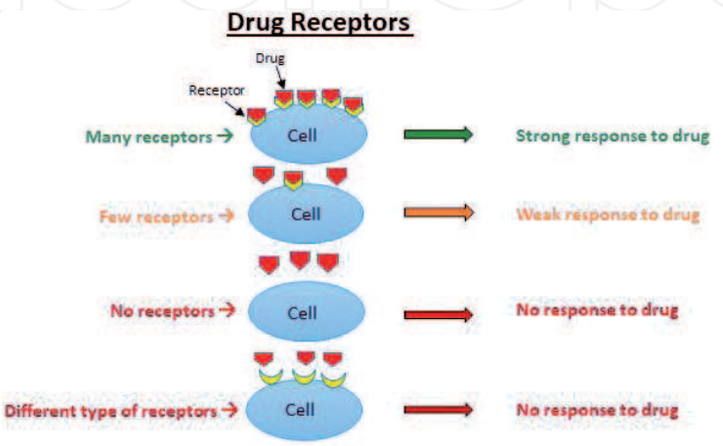

Figure 1.
Patient response relative to drug-receptor interactions and receptor availability.

receptor 2 (HER2) receptor. Some breast cancers make too much HER2 and this extra HER2 helps the cancer develop and spread. T-DM1 has shown potential activity in this subset of patients in small clinical series because it works by attaching to HER2 on cancerous cells and killing them. In terms of receptor availability, this mean if a patient tumor has a high amount of HER2 (HER2 positive), the doctor may prescribe T-DM1; but if the tumor does not have enough HER2 (HER2 negative), T-DM1 will not work for such a patient [8].

1.1.2 Drug uptake

Some drugs have receptor inside the cells or receptor binding sites on the inside part of the target cell. Therefore these drugs need to be actively taken into the tissues and cells in which they act. The ability and the rate of a cell to uptake the drug is determined by that cell's genetic makeup. The genetic makeup can also affect how quickly some drugs are removed from the cells in which they act and if drugs are pumped out from the cell too quickly, they might not have time to elicit observed effect. Decreased uptake can mean that the drug does not work as well and can cause it to build up in other parts of your body, which can cause problems (refer to **Figure 2** below) [2].

For instance, in the treatment of dyslipidaemia (high cholesterol and/or fats levels in blood) drugs called statins are used to reduce cholesterol from the liver and these drugs are known to cause muscle problems. Intake of simvastatin for the disease requires that the drug be taken up into the liver by the protein encoded by SLCO1B1 gene. Some people have a specific change in this gene that causes less of simvastatin to be taken into the liver. Intake of high doses of simvastatin could lead to build up of the drug in the muscles, causing muscle weakness and pain. Therefore prior to prescribing simvastatin, genetic testing of SLCO1B1 gene to check if simvastatin is the best statin for use is key [9].

1.1.3 Drug breakdown

Genetic factors that influence enzyme levels account for differences in drug breakdown, giving rise to "genetic polymorphisms" in drug metabolism. If the patient breaks the drug down more quickly than most people, the body gets rid of the drug faster and the patient might need more of the drug or a different drug; lesser if the body breaks the drug down more slowly as illustrated in **Figure 3** below.

Metabolic reactions mediated by P450 phase I enzymes typically modify functional groups (–OH, –SH, $–NH_2$, $–OCH_3$) of endogenous and exogenous compounds (drugs), resulting in an alteration of the biological activity of the compound. Phase I enzymes are involved in the metabolism of over 75% of prescription drugs; therefore, polymorphisms in these enzymes may significantly affect blood levels, which in turn may alter response to many drugs [10].

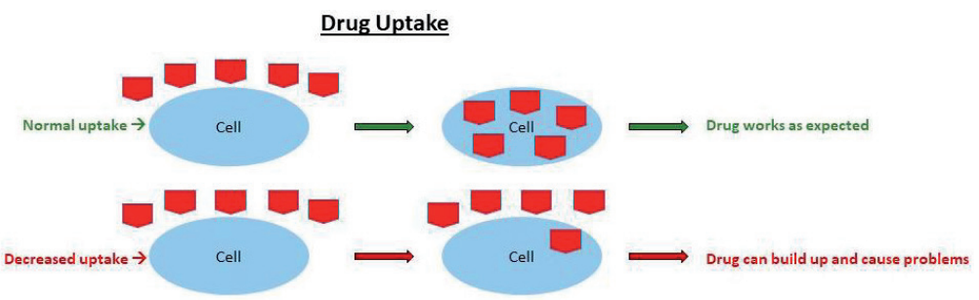

Figure 2.
Differences in drug uptake and potential accumulation leading to toxicity.

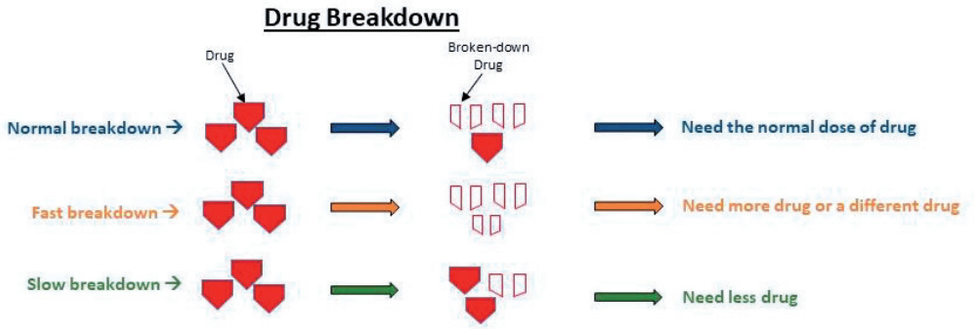

Figure 3.
Rates of drug metabolism.

1.2 The impact of pharmacogenomics on medical treatment

Pharmacogenomics provides a better understanding the reasons behind the differing responses of a drug by individuals. The discovery of genetic variation and its associated response variation to a drug, provide the basis for recommending a drug regimen to an individual patient. Genetic makeup-based prescription, design, and implementation of therapy do not only improve the outcome of treatments, but also reduce the risk of toxicity and other adverse events. Therefore genetic testing promotes a better understanding of individual variations and their effect on drug response, metabolism excretion, toxicity and this will replace the trial-and-error approach of treatment which is a common practice [11]. Pharmacogenomics promote personalized medicine instead.

1.3 Biomarkers and "core" essential drugs

The **Table 1** below is a summary of "core list"essential medicines identified from the 21st WHO EML updated in June 2019 [5] presented against the corresponding biomarkers and therapeutic areas from the USFDA Table of Pharmacogenomic Biomarkers in Drug Labeling updated in June 2020 [6].

2. Clinical pharmacogenomics of the biomarkers and implicated drugs

2.1 Cytochrome p450 isozymes

Polymorphic cytochrome P450 isozymes, CYP2C9, CYP2C19 and CYP2D6 in particular, mediate approximately 40% of P450-oxidative drug metabolism, which makes drug dosing problematic. Generally four genetically different types of individuals have been identified, namely:

1. Poor metabolizers (PMs), who lack the functional enzyme;

2. Intermediary metabolizers (IMs), who are heterozygous for one deficient allele or carry two alleles that cause reduced enxyme activity;

3. Extensive metabolizers (EMs), who have two normal alleles; and

4. Ultrarapid metabolizers (UMs), who have two have multiple gene copies, a trait that is dominantly inherited.

Biomarker	Drug (s)	Therapeutic area
CYB5R	Metoclopramide	Gastroenterology
CYP2B6	Efavirenz	Infectious diseases
CYP2C19	Clopidogrel	Cardiology
	Diazepam	Neurology
	Ethinyloestradiol	Gynaecology
	Omeprazole	Gastroenterology
	Voriconazole	Infectious diseases
CYP2C9	Phenytoin	Neurology
	Warfarin	Hematology
CYP2D6	Amitryptilline	Psychiatry
	Codeine	Anaesthesiology
	Fluoxetine	Psychiatry
	Ondansetron	Gastroenterology
	Risperidone	Psychiatry
	Quinine	Infectious diseases
DYPD	fluorouracil	Oncology
G6PD	Ascorbic acid	Gastroenterology
	Ceftriaxone	Infectious diseases
	Chloroquine	Infectious diseases
	Erythromycin	Infectious diseases
	Nitrofurantoin	Infectious diseases
	Potassium chloride	Gastroenterology
	Primaquine	Infectious diseases
	Sulfasalazine	Gastroenterology
	Sodium chloride	Gastroenterology
	Sulfadiazine	Infectious diseases
	Tetracaine	Anaesthesiology
	Quinine	Infectious diseases
	Sulfamethoxazole	Infectious diseases
	Trimethoprim	Infectious diseases
	Dapsone	Infectious diseases
HLA-B	Abacavir	Infectious diseases
	Carbamazepine	Psychiatry
IFNL3 (IL28B)	Daclatasavir	Infectious diseases
	Dasabuvir	Infectious diseases
	Ledipasvir	Infectious diseases
	Ombitasvir	Infectious diseases
	Paritaprevir	Infectious diseases
	Ritonavir	Infectious diseases
	Sofosbuvir	Infectious diseases

Biomarker	Drug (s)	Therapeutic area
Nonspecific (Congenital Methemoglobinemia)	Dapsone	Infectious diseases
	Lidocaine	Anaesthesiology
Nonspecific (Genetic Susceptibility to Malignant Hyperthermia)	Isoflurane	Anaesthesiology
Nonspecific (NAT)	Sulfamethoxazole	Infectious diseases
	Trimethoprim	Infectious diseases
	Hydralazine	Cardiology
	Sodium Nitrite	Toxicology
POLG	Valproic acid	Neurology
PROC1	Warfarin	Hematology
	Estradiol	Gynaecology
SERPINC1 (Antithrombin III)	Progesterone	Gynaecology
UGT1A1	Dolutegravir	Infectious diseases
	Raltegravir	Infectious diseases
VKORC1	Warfarin	Hematology

Table 1.
Biomarkers, "core" essential drugs and their therapeutic areas.

Polymorphism of cytochrome P450 metabolizing enzymes has the greatest effect on inter individual variability of drug response. These polymorphisms affect the response of individuals to drugs used in the treatment of diseases not limited to cardiology, hematology, neurology, psychiatry, gynaecology, gastroenterology, anaesthesiology and infectious diseases [12].

The effect on CYP2C9 on warfarin dosing has been evident. Individuals who are heterozygous for a *2 allele and *3 allele of CYP2C9 would require, on average, a 21% and 34% lower daily dose of warfarin for maintenance, respectively; than homozygous wild-type patients, and individuals who are homozygous for the *2 allele or the *3 allele require a 60–75% lower dose of warfarin than homozygous wild-type patients [13].

CYP2D6 is responsible for the metabolism of most psychoactive drugs, including the tricyclic antidepressants and the dosage required corresponds closely with the CYP2D6 phenotype. The kinetics of nortriptyline is dependent on the number of active CYP2D6 genes and the dosage required to reach the same plasma levels varies from 30 to 50 mg in PMs to 500 mg in UMs [14].

The majority of phenytoin metabolism is done by CYP2C9 and effective dosing of phenytoin is highly linked to the CYP2C9 genotype. Several examples of adverse effects of phenytoin, including CNS intoxication and other neurological symptoms, have been described in patients with defective CYP2C9 alleles following phenytoin treatment [15].

Dosing with proton pump inhibitors to reach a therapeutic drug plasma concentration highly depends on the CYP2C19 phenotype. A study conducted using a low dose omeprazole (20 mg) to treat ulcers, revealed very low cure rates in EMs (25%), higher in IMs (50%) and complete in PMs (100%), illustrating the necessity of higher plasma levels for effective treatment [16].

CYP2B6 polymorphisms can affect the pharmacokinetics and therapeutic outcome of anti-HIV agents, such as efavirenz, which is a substrate of CYP2B6. The CYP2B6*6 allele harboring the 516G > T (Q172H) and 785A > G (K262R) was

significantly associated with a pronounced decrease in CYP2B6 expression and activity. CYP2B6 genetic polymorphisms markedly influence the metabolism of efavirenz in human liver microsomes [17].

2.2 Cytochrome b5 reductases (CYB5R)

Patients with NADH-cytochrome b5 reductase deficiency, encoded by CYB5R1, CYB5R2, CYB5R3 and CYB5R4 genes, are at an increased risk of developing methemoglobinemia and/or sulfhemoglobinemia when metoclopramide is administered. Additionally, neonates have reduced levels of NADH-cytochrome b5 reductase and prolonged drug clearance, and therefore are also more susceptible to methemoglobinemia [18].

2.3 Non-cytochrome p450 enzymes

2.3.1 Vitamin K epoxide reductase complex subunit 1 (VKORC1)

The wide variation in warfarin dose highlights the heterogeneity amongst patients in therapeutic response to warfarin. A study conducted by Harrington *et al*. demonstrated that a heterozygous 196G → A transition that predicted a Valine-66 Methionine substitution in the VKORC1 polypeptide is the cause of warfarin resistance [19]. VKORC1 polymorphisms can significantly changes pharmacodynamics and maintenance dose requirements for warfarin. Patients with the 1639A (rs992323) and 1173 T (rs9934438) allele require a lower warfarin dose compared with patients with 9041A (rs7294) allele rather need a higher warfarin dose. Incorporating VKORC1 and CYP2C9 genotype information into the warfarin dosing equation holds great promise to select the optimal dose for the individual patient at the start of warfarin therapy [20].

2.3.2 Glucose-6-Phosphate Dehydrogenase (G6PD)

G6PD deficiency is an X-linked genetic disorder with 187 known allelic mutations. G6PD is a critical enzyme in the pentose phosphate pathway. G6PD deficiency exhibits diminished activity in these patients, leading to inadequate production of protective intracellular thiols during oxidative stress. The deficiency makes erythrocytes more vulnerable to oxidative stress and has been associated with neonatal hyperbilirubinemia, acute hemolysis, and chronic nonspherocytic hemolytic anemia [21]. Some drugs should be avoided by all G6PD-deficient patients: these include primaquine, nitrofurantoin, and dapsone; while others like IV ascorbic acid, chloroquine and quinine should be used with caution.

2.3.3 Uridine diphosphate-glucuronosyltransferase 1A1 (UGT1A1)

Dolutegravir (DTG) is metabolized mainly by UGT1A1. Individuals carrying UGT1A1*6 and/or UGT1A1*28 polymorphs were demonstrated to be associated with high DTG trough concentrations, and that carrying UGT1A1*6 and/or UGT1A1*28 alleles might be a risk factor for neuropsychiatric adverse events [22]. HIV-1 infected patients demonstrated significant impact of UGT1A1*28 variant on raltegravir exposure with UGT1A1*28 carriers showing higher raltegravir plasma levels and lower metabolic ration when compared to UGT1A1*1/*1 carriers. This effect appeared to be allele-dose dependent. This pharmacokinetic effect did not correlate with any clinical adverse events or biological abnormalities except for the sensation of fatigue. Some virological failures have been associated with low

raltegravir exposure; hence UGT1A1*28 genotyping may still be considered as an interesting tool to improve raltegravir therapy particularly when risk factors for virological failure are present, such as high viral load at baseline, once daily regimen or when raltegravir is used to replace high genetic barrier drug in treatment-exposed patients [23].

2.3.4 Human leukocyte antigen B (HLA-B)

Abacavir-induced hypersensitivity reaction has been associated with the presence of the major histocompatibility complex class I allele HLA-B*5701. A screening test for the HLA-B*5701 allele can assist clinicians to identify patients who are at risk of developing a hypersensitivity reaction to abacavir. Abacavir hypersensitivity reaction affects 5 to 8% of patients and can be observed during the first 6 weeks of antiretroviral therapy [24]. Relatively high incidence of HLA-B*1502 in many Asian populations has resulted in the FDA's decision to recommend testing for all Asians prior to initiating carbamazepine. Han Chinese who have the HLA-B*1502 allele are at a much increased risk of developing Stephen-Johnsons Syndrome/ Toxic Epidermal Necrolysis (SJS/TEN) when exposed to carbamazepine [25].

2.3.5 Interferon Lambda 3 (Interleukin-28B)

Sofosbuvir is a potent nucleotide hepatitis C virus (HCV) Nonstructural protein 5B (NS5B) polymerase inhibitor that is also a P-glycoprotein (encoded by the ABCB1 gene) substrate. Sofosbuvir is metabolized mainly into GS-331007 in the liver. ABCB1 gene (3435 CT/TT and 1236 TT genotypes) are the predictors of GS-331007 concentrations [23]. P-glycoprotein (P-gp) removes chemical toxins and metabolites (including GS-331007) from cells into bile, urine and the intestinal lumen. Alterations in P-gp function may affect the bioavailability, distribution and clearance of many drugs [26]. The genetics of IL28B have played an important role in predicting outcome and toxicity of HCV polymerase inhibitors.

2.3.6 DNA polymerase gamma (POLG)

DNA polymerase gamma (POLG) determines the risk of sodium valproate induced liver toxicity. Rare mutations in POLG, which codes for the mitochondrial DNA polymerase gamma, cause the Alpers-Huttenlocher syndrome (AHS); a neuro-metabolic disorder associated with an increased risk of developing fatal sodium valproate hepatotoxicity [27]. Thus, sequencing the POLG gene remains the best diagnostic test to prevent sodium valproate-induced liver failure and patient death.

2.4 Clotting factors

2.4.1 Protein C, inactivator of coagulation factors Va and VIIIa (PROC, PROC1)

PROC encodes for vitamin K-dependent plasma glycoprotein called Protein C. The protein is cleaved to its active form by the thrombomodulin-thrombin complex. The activated form contains a serine protease domain and functions in degradation of the active forms of coagulation factors V and VIII. Mutations of this gene have been associated with thrombophilia due to protein C deficiency and recurrent venous thrombosis [28].

2.4.2 SERPINC1 (Antithrombin III)

The gene SERPINC1 encodes a serine protease inhibitor named antithrombin III (ATIII). Antithrombin III is the most important coagulation factor inhibitor, and even minor changes in ATIII can significantly alter the risk of thromboembolism. The incidence of ATIII-inherited deficiency is relatively rare in the general population but in patients with thromboembolism, the prevalence of ATIII deficiency ranges from 0.5–5%. Acquired deficiency of ATIII can be found in patients on oral contraceptives (progesterone). In overall, patients with the acquired type of ATIII deficiency are exposed to a high risk of thromboembolism, due to depletion of coagulation factor inhibitor critical to anticoagulation in plasma [29, 30].

2.5 Dihydropyrimidine dehydrogenase (DYPD)

The dihydropyrimidine dehydrogenase, encoded by DPYD gene, is an enzyme that catalyzes the rate-limiting step in fluorouracil metabolism. Genetic variations in the DPYD gene can lead to enzymes with reduced or no activity. Individuals who have at least one copy of a non-functional DPYD variant especially the DPYD*2A or DPYD*13, will not be able to metabolize fluorouracil at normally. As a result, these individuals are at risk of potentially life-threatening toxicity to fluorouracil including bone marrow suppression and neurotoxicity. The prevalence of dihydropyrimidine dehydrogenase partial deficiency is approximately 35%; although it varies in different populations. Complete absence of this enzyme function is often fatal with exposure to 5-FU chemotherapy [31].

2.6 Biomarkers inducing genetic susceptibility to diseases

Younker et al. reported a G6PD deficient 22-month-old baby who suffered Malignant Hyperthermia (MH). They concluded that decreased major antioxidant system activity may cause susceptibility to MH [32]. Altikat et al. found that isoflurane has an inhibitory effect on G6PD activity; thus predisposing anaesthesized patient to developing MH [33]. Malignant hyperthermia is a pharmacogenetic disorder in the regulation of calcium in skeletal muscles which is related to an uninhibited muscle hypermetabolic reaction to potent inhalation agents such as isoflurane.

Methemoglobin is an aberrant form of hemoglobin arising from oxidation of iron in the normal heme molecule from the ferrous form (Fe^{2+}) to the ferric (Fe^{3+}) form. The presence of ferric heme molecules causes a structural change in the hemoglobin molecule, resulting in reduced oxygen-carrying capacity and impaired unloading of oxygen at the tissue; resulting in left shift in the oxygen saturation curve causing functional anemia referred to as methemoglobinemia. While methemoglobinemia can be congenital and should be considered in cyanotic infants, it is more often an adverse medication effect, most commonly related to dapsone use. Dapsone most commonly causes methemoglobin, but other offending drugs include the local anesthetics such as lidocaine [34].

3. Conclusion

There is a correlation between individual genetic makeup and the pharmacological response to drugs. Genetic variation plays a pivotal role in the efficacy and safety of different drugs. Thus gene testing prior to initiating concerned treatment is the

best clinical practice that will eliminate the "one size fits all" approach and promote personalized approaches that consider individual genetic makeup in attempt to enhance the efficacy and safety of drugs.

4. Future aspects

The future has that the putting in place proper technologies to perform gene testing in clinical settings will be of great help in individualizing treatment to patients. However, genetic polymorphism varies between populations; therefore further research needs to be done on different populations so that gene testing technologies will focus on respective populations.

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