Personalized Medicine: Pharmacogenomics and Drug Development

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Received: 15 Sep. 2016; Revised: 10 Oct. 2016; Accepted: 05 Dec. 2016

Abstract- Personalized medicine aims is to supply the proper drug to the proper patient within the right dose. Pharmacogenomics (PGx) is to recognize genetic variants that may influence drug efficacy and toxicity. All things considered, the fields cover a wide area, including basic drug discovery researches, the genetic origin of pharmacokinetics and pharmacodynamics, novel drug improvement, patient genetic assessment and clinical patient administration. At last, the objective of Pharmacogenomics is to anticipate a patient's genetic response to a particular drug as a way of presenting the best possible medical treatment. By predicting the drug response of an individual, it will be possible to increase the success of therapies and decrease the incidence of adverse side effect.

Acta Med Iran 2017;55(3):150-165.

Keywords: Personalized medicine; Pharmacogenetics; Drug discovery; Drug safety

Introduction

The proper drug for the proper patient for the right period of time is the principle object of personalized medicine (PM). Therefore, PM refers to "the management of a patient's disease or disposition by utilizing the best molecular knowledge to accomplish the best medical result for that individual." PM is the base of global health. Indeed, the steady rise in life hopes worldwide since the discovery of penicillin owes it to a succession of innovative medicines (1-3).

During the prior decade, drug improvement has become expensive and ineffective, with a likelihood of accomplishment averaging 10% (4). This is often the results of higher safety barriers needed for restrictive approval in an exceeding health care atmosphere much more advanced than we tend to ever imaginary before the completion of Project Human Genome Project. However, despite detailed regulatory fastidiousness, adverse drug reactions still occur that eventually lead to the withdrawal of drug products (4-10). PM has the ability of restricted this gap in drug safety between what is planned from clinical trials and what really happen in custom. Furthermore, by centering on the patient's necessities, before on only the features of the drug outcome or the illness, we may be competent to expand the proficiency of future drug advancement (1,11-16).

The international interest with PM is boosted by huge progress in genomics, containing the view of resequencing of total genomes at the population stage for a modest fee. The impression of genomics can be surveyed within either genetic mutations of a constitutive protein in the target cell (17) or the proteins responsible for the distribution, absorption, metabolism and removal of the drug (pharmacogenomics pathway) (18). Examples of the earlier path contain the tyrosine phosphatase inhibitors in the therapy of chronic myelogenous leukemia and the monoclonal antibody trastuzumab against HER-2, the human epidermal growth factor receptor that is overexpressed in individual breast cancer cells.

Examples of the last path contain genetic polymorphisms of the cytochrome C drug metabolizing enzymes (19) for instance CYP3A4, CYP2D6 (19) P-glycoprotein and multidrug resistance protein (20). In this be trained, we need to do not forget the value and position of pharmaceutical industries, FDA, NIH, etc. In the development and production of the drug, in order to reach PM objectives.

Pharmacogenetics

Pharmacogenetics reputation acceptable in

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pharmacology within the pre-genomic of existence is the reassessment of the liveliness of genetic factors on the action of medications as opposed to genetic causes of illness. Outburst it is the estimate of the group among the individual's genotype and the individual's capability to metabolize a far-off compound. The pharmacological accomplish of an antivenin depends on the pharmacodynamics. It is aside from covers the impact of several factors on these processes. Counterirritant metabolism is the duo of the consummate determinants of remedy clearance and the issue range is maximum answerable for interindividual variations in pharmacokinetics. The variances in acceptance to medications are often crap-shooter between members of a population than they are within the identical person or among monozygotic twins at distinct periods. It is a ballpark that genetics account for 20-95% of the variability in medication nature and results.

The role of pharmacogenetics in pharmaceutical industry

Gene's involve pharmacodynamics and pharmacokinetics. Sequence variation meditation nature, genes adjust the pharmacokinetics of a medication, whereas sequence variant in medication target genes can replace the pharmacodynamics of the medication Pharmacogenetics has a three-fold companionship in the pharmaceutical industry, which is be fitted to the expand PM: 1) for evaluate the medication metabolism and pharmacological results; 2) for calculating genetically determined adverse reactions and 3) drug discovery and development and as an assist to arranging clinical trial.

Pharmacogenomics

Pharmacogenomics (PGx) is momentous for PM, because different patients respond differently to a similar drug. These dissimilarities are frequently more between participants of a population than they are inside the identical one on another period (or between monozygotic twins) (20). The existence of huge population variances through little interpatient variability is reliable with a legacy as a cause of drug reply; it is assessed that genetics can report for 20 to 95 percent of the variability in drug nature and outcomes (21-23). While various nongenetic aspects inspiration the outcomes of drugs, containing age, organ function, related therapy, drug connections, and the nature of the illness, there are now abundant instances of items into which inter-individual alterations in drug reaction are due to sequence variants in genes encoding drug-metabolizing enzymes, drug carriers, or drug targets (12,24-27). Pharmacogenomics stays the analysis of how human genetic variants involve an individual's reaction to drugs, with emphasis on drug metabolism, absorption, and distribution (22,28). Pharmacogenomics performs a notable function inside finding drug reactant and non-reactant, preventing side effects, and improving medication dose (7,30). Lately, FDA has developed a strong pharmacogenomics promoter in an attempt to prepare medications safer and further valuable (29-31). So as to adjust the property of now promoted medications, the FDA has appraised clear drug labels to contain PGx data. Presently, over one hundred FDA-approved medications take PGx data on their labels that define genes responsible for medication display, clinical reaction variability, and the possibility of adverse events (32).

Pharmacogenetics assays

The fundamental project in pharmacogenetics is providing an analysis procedure for clinical estimation of a patient's eventual response to a drug. Though, the organization a research assay to evaluate a DNA sample is possible, the progress of an assay for the employment in a clinical atmosphere has colossal bigger standards. Above all a valuable scientific estimation must include the next subjects:

- Development in a medically primary foremost response; a scan have to now not only observe a DNA sequence that's expressive of a response, however that response needs to have scientific importance such that a greater choice can be made that might in any other case be viable.
- Limited false positives (efficacy-based assay) and negatives (safety-based assay); when non-responder recognized as a responder, it is false positive and it is a test for drug efficacy. A false negative in a test for safety and the patients at risk identified as not at risk. An appropriate test must have a low false positive rate, but can withstand a moderate frequency of false negative. Although the response rate in the optimized group didn't be 100% to be valuable. In the case of safety test is necessary to recognize maximum, if not all, patients at risk for the adverse side effect then false negatives should be very low. A high rate of false positive can withstand since such adverse events are infrequent in most drugs.
- Explainable and clinically applicable results; because of the genotyping tests are complex, and explanation of the outcomes needs an extreme level of methodical information and due to clinicians are not molecular geneticists and not they be, thus an application analyze must be informal to usage in a

predictable medical setting, and should offer outcomes that can be recognized by the physician and relied on by the patient. The assessments must be streamlined to the highest step probable, and clarification devices, whether computer algorithms, must be accessible. Extremely complicated investigates, such as various polymorphism analyses (DNA chips) or gene expression analysis will be mainly challenging.

Pharmacogenomics and drug discovery

The effect on of recently applied sciences at quite a lot of stage of the drug discovery system is shown schematically in Figure 1. This scheme proposes that genomic technologies and pharmacogenomics show major role in drug discovery and develop. Analysis of SNP data has already caused in the detection of a number of precandidate genes probably suitable for drug discovery. Know-how got from learning of the act of genes, their interactions, their function in organic paths, in addition to their variability among the populace will also be employed in drug discovery. A working out of genes expression changes from ordinary tissues via the sickness development process amongst extraordinary populations supplies possible goals for drug progress. Goal determination sooner or later will have to be genetics-centered alternatively than the presently popular target validation. Use of genetic proof-established approaches of goal decision must cut back the trying out of too many hypotheses which can be finally proven flawed. Reducing attrition and bettering a product's return on funding measure success in discovery. As molecules cross by way of the progress pipelines, selections made in 2020 will definitely perform a role within the effects in 2025.

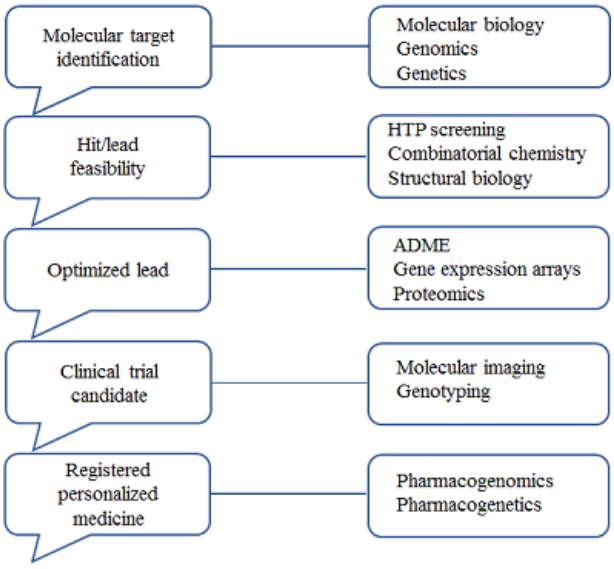

Figure 1. Influence of novel technologies at different steps of the drug discovery process

Pharmacogenomics biomarkers in drug labeling

Scientific product labeling must furnish enough knowledge concerning the product and its usage. Medication labeling for illustration is "planned to present abstract of the substantive scientific knowledge required for the comfortable and helpful application of medicines. FDA obliges product labeling to be stabilized, scientifically exact and no longer misleading, and that clear instruction is communicated to healthcare practitioners for medication ordering and/or administration. PM that will best be faithful and strong in unique sub-populations or need to be directed in extraordinary doses in one-of-a-kind sub-populace should be labeled as an outcome.

Pharmacogenomics can play a principal role in opting for responders and non-responders to medications, warding off opposed events, and optimizing drug dose. Drug labeling may just contain know-how on genomic biomarkers and may describe:

- Medication revelation and clinical reply variability
- Possibility for adverse results
- Genotype-particular mediating
- Structures of medication action
- Polymorphic medication target and nature genes

An indication of 1200 medication labels of FDA-approved drugs in the USA from 1945 to 2005 revealed that 121 covered pharmacogenomics data (30). The study

concluded that incorporation and suitable use of pharmacogenomics understanding in drug labels must be proven for its capacity to toughen medications use and defense in the US. Presently, there are labels for >141 FDA-accredited medicines that include pharmacogenomics biomarker expertise. There's a need for increasing this number.

The table 1 inclines FDA-Approved medication with pharmacogenomics know-how in their labeling. The labeling for some, however now not all, involves definite trials to be taken the biomarker data. Pharmacogenomics know-how can show dissimilar parts of the labeling depending on the activities. This table does not cover non-human genetic biomarkers (e.g., microbial versions that influence sensitivity to antibiotics), or biomarkers which can be consumed entirely for diagnostic principles (e.g., for genetic ailments) until they're linked to medication exercise or used to verify a particular subset in whom advocating capability argues. For medications which might be accessible in further than one dosage ranges, salts, or mixtures, a single consultant product is listed. Within the case of combination products, the only agent associated with the biomarker is listed unless the agent is most operatives approved as a combination product, where case all agents are listed.

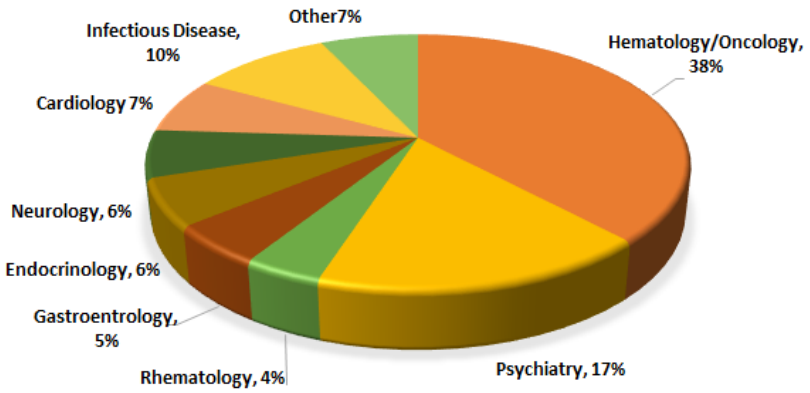

Figure 2. Pharmacogenomic biomarker information in drug labeling

Table 1. Pharmacogenomic biomarkers in drug labeling (cont.)

Drug	Therapeutic area	Biomarker	Referenced subgroup	Labeling sections
Abacavir	Infectious Diseases	HLA-B	HLA-B*5701 allele carriers	Boxed Warning, Contraindications, Warnings and Precautions
Ado-TrastuzumabEmtansine	Oncology	ERBB2	HER2 protein overexpression or gene amplification positive	Indications and Usage, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Afatinib	Oncology	EGFR	EGFR exon 19 deletion or exon 21 substitution (L858R) positive	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Alectinib	Oncology	ALK	ALK gene rearrangement positive	Indications and Usage, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Alirocumab	Endocrinology	LDLR	LDL receptor mutation heterozygotes	Indications and Usage, Adverse Reactions, Clinical Studies
Amitriptyline	Psychiatry	CYP2D6	CYP2D6 poor metabolizers	Precautions
Anastrozole	Oncology	ESR1, PGR	Hormone receptor positive	Indications and Usage, Adverse Reactions, Drug Interactions, Clinical Studies
Arformoterol [1]	Pulmonary	UGT1A1	UGT1A1 poor metabolizers	Clinical Pharmacology
Arformoterol [2]	Pulmonary	CYP2D6	CYP2D6 intermediate or poor metabolizers	Clinical Pharmacology

Continuance of Table 1.

Aripiprazole	Psychiatry	CYP2D6	CYP2D6 poor metabolizers	Dosage and Administration, Use in Specific Populations, Drug Interactions, Clinical Pharmacology
Aripiprazole Lauroxil	Psychiatry	CYP2D6	CYP2D6 poor metabolizers	Dosage and Administration, Use in Specific Populations, Clinical Pharmacology
Arsenic Trioxide	Oncology	PML-RARA	PML-RARα translocation positive	Clinical Pharmacology, Indications and Usage
Atomoxetine	Psychiatry	CYP2D6	CYP2D6 poor metabolizers	Dosage and Administration, Warnings and Precautions, Drug Interactions, Clinical Pharmacology
Azathioprine	Rheumatology	TPMT	TPMT intermediate or poor metabolizers	Clinical Pharmacology, Warnings, Precautions, Drug Interactions, Adverse Reactions, Dosage and Administration
Belinostat	Oncology	UGT1A1	UGT1A1*28 allele homozygotes	Dosage and Administration, Clinical Pharmacology
Blinatumomab	Oncology	BCR-ABL1	Philadelphia chromosome negative	Indications and Usage, Clinical Studies
Boceprevir	Infectious Diseases	IFNL3	IL28B rs12979860 T allele carriers (C/T and T/T genotype)	Clinical Pharmacology
Bosutinib	Oncology	BCR-ABL1	Philadelphia chromosome positive	Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Studies
Brexpiprazole	Psychiatry	CYP2D6	CYP2D6 poor metabolizers	Dosage and Administration, Drug Interactions, Use in Specific Populations, Clinical Pharmacology
Busulfan	Oncology	BCR-ABL1	Philadelphia chromosome negative	Clinical Studies
Cabozantinib	Oncology	RET	RET mutation positive	Clinical Studies
Capecitabine	Oncology	DPYD	DPD deficient	Warnings and Precautions, Patient Counseling Information
Carbamazepine (1)	Neurology	HLA-B	HLA-B*1502 allele carriers	Boxed Warning, Warnings, Precautions
Carbamazepine (2)	Neurology	HLA-A	HLA-A*3101 allele carriers	Warnings
Carglumic Acid	Inborn Errors of Metabolism	NAGS	N-acetyl glutamate synthase deficient	Indications and Usage, Warnings and Precautions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies
Carisoprodol	Rheumatology	CYP2C19	CYP2C19 poor metabolizers	Use in Specific Populations, Clinical Pharmacology
Carvedilol	Cardiology	CYP2D6	CYP2D6 poor metabolizers	Drug Interactions, Clinical Pharmacology
Celecoxib	Rheumatology	CYP2C9	CYP2C9 poor metabolizers	Dosage and Administration, Use in Specific Populations, Clinical Pharmacology
Ceritinib	Oncology	ALK	ALK gene rearrangement positive	Indications and Usage, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Cetuximab (1)	Oncology	EGFR	EGFR protein expression positive	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Cetuximab (2)	Oncology	KRAS	KRAS codon 12 and 13 mutations negative	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Cevimeline	Dental	CYP2D6	CYP2D6 poor metabolizers	Precautions
Chloroquine	Infectious Diseases	G6PD	G6PD deficient	Precautions
Chlorpropamide	Endocrinology	G6PD	G6PD deficient	Precautions

Continuance of Table 1.

Cholic Acid	Inborn Errors of Metabolism	AKR1D1, HSD3B7, CYP27A1, AMACR, CYP7A1	Bile acid synthesis enzyme deficient	Indications and Usage, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies
Cisplatin	Oncology	TPMT	TPMT intermediate or poor metabolizers	Adverse Reactions
Citalopram (1)	Psychiatry	CYP2C19	CYP2C19 poor metabolizers	Clinical Pharmacology, Warnings, Dosage and Administration
Citalopram (2)	Psychiatry	CYP2D6	CYP2D6 poor metabolizers	Clinical Pharmacology
Clobazam	Neurology	CYP2C19	CYP2C19 poor metabolizers	Dosage and Administration, Use in Specific Populations, Clinical Pharmacology
Clomipramine	Psychiatry	CYP2D6	CYP2D6 poor metabolizers	Precautions
Clopidogrel	Cardiology	CYP2C19	CYP2C19 intermediate or poor metabolizers	Boxed Warning, Dosage, and Administration, Warnings and Precautions, Clinical Pharmacology
Clozapine	Psychiatry	CYP2D6	CYP2D6 poor metabolizers	Dosage and Administration, Use in Specific Populations, Clinical Pharmacology
Cobimetinib	Oncology	BRAF	BRAF V600E/K mutation-positive	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Codeine	Anesthesiology	CYP2D6	CYP2D6 ultrarapid metabolizers	Boxed Warning, Warnings and Precautions, Use in Specific Populations, Patient Counseling Information
Crizotinib	Oncology	ALK	ALK gene rearrangement positive	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Dabrafenib (1)	Oncology	BRAF	BRAF V600E/K mutation-positive	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies, Patient Counseling Information
Dabrafenib (2)	Oncology	G6PD	G6PD deficient	Warnings and Precautions, Adverse Reactions, Patient Counseling Information
Dapsone (1)	Dermatology	G6PD	G6PD deficient	Warnings and Precautions, Use in Specific Populations, Patient Counseling Information
Dapsone (2)	Infectious Diseases	G6PD	G6PD deficient	Precautions, Adverse Reactions, Overdosage
Dasatinib	Oncology	BCR-ABL1	Philadelphia chromosome positive, T315I mutation positive	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies
DenileukinDiftitox	Oncology	IL2RA	CD25 antigen positive	Indications and Usage, Warnings and Precautions, Clinical Studies
Desipramine	Psychiatry	CYP2D6	CYP2D6 poor metabolizers	Precautions
Dexlansoprazole	Gastroenterology	CYP2C19	CYP2C19 poor metabolizers	Drug Interactions, Clinical Pharmacology
Dextromethorphan and Quinidine	Neurology	CYP2D6	CYP2D6 poor metabolizers	Warnings and Precautions, Clinical Pharmacology
Diazepam	Neurology	CYP2C19	CYP2C19 poor metabolizers	Clinical Pharmacology
Dinutuximab	Oncology	MYCN	MYCN amplification positive	Clinical Studies
Dolutegravir	Infectious Diseases	UGT1A1	UGT1A1 poor metabolizers	Clinical Pharmacology
Doxepin (1)	Psychiatry	CYP2D6	CYP2D6 poor metabolizers	Clinical Pharmacology
Doxepin (2)	Psychiatry	CYP2C19	CYP2C19 poor metabolizers	Clinical Pharmacology

Continuance of Table 1.

Drospirenone and Ethinyl Estradiol	Gynecology	CYP2C19	CYP2C19 intermediate metabolizers	Clinical Pharmacology
Eliglustat	Inborn Errors of Metabolism	CYP2D6	CYP2D6 ultrarapid, intermediate or poor metabolizers	Indications and Usage, Dosage and Administration, Contraindications, Warnings and Precautions, Drug Interactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies
Elosulfase	Inborn Errors of Metabolism	GALNS	N-acetylgalactosamine-6-sulfatase deficient	Indications and Usage, Warnings and Precautions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies
Eltrombopag (1)	Hematology	F5	Factor V Leiden carriers	Warnings and Precautions
Eltrombopag (2)	Hematology	SERPINC1	Antithrombin III deficient	Warnings and Precautions
Erlotinib (1)	Oncology	EGFR	EGFR protein expression positive	Clinical Studies
Erlotinib (2)	Oncology	EGFR	EGFR exon 19 deletion or exon 21 substitution (L858R) positive	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Escitalopram (1)	Psychiatry	CYP2D6	CYP2D6 poor metabolizers	Drug Interactions
Escitalopram (2)	Psychiatry	CYP2C19	CYP2C19 poor metabolizers	Adverse Reactions
Esomeprazole	Gastroenterology	CYP2C19	CYP2C19 poor metabolizers	Drug Interactions, Clinical Pharmacology
Everolimus (1)	Oncology	ERBB2	HER2 protein overexpression negative	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Drug Interactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies
Everolimus (2)	Oncology	ESR1	Estrogen receptor positive	Clinical Studies
Evolocumab	Endocrinology	LDLR	LDL receptor mutation heterozygotes and homozygotes	Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Studies
Exemestane (1)	Oncology	ESR1	Estrogen receptor positive	Indications and Usage, Dosage and Administration, Clinical Studies
Exemestane (2)	Oncology	PGR	Progesterone receptor positive	Clinical Studies
Fesoterodine	Urology	CYP2D6	CYP2D6 poor metabolizers	Drug Interactions, Clinical Pharmacology
Fluorouracil (1)	Dermatology	DPYD	DPD deficient	Contraindications, Warnings
Fluorouracil (2)	Oncology	DPYD	DPD deficient	Warnings
Fluoxetine	Psychiatry	CYP2D6	CYP2D6 poor metabolizers	Warnings and Precautions, Drug Interactions, Clinical Pharmacology
Flurbiprofen	Rheumatology	CYP2C9	CYP2C9 poor metabolizers	Clinical Pharmacology
Fluvoxamine	Psychiatry	CYP2D6	CYP2D6 poor metabolizers	Drug Interactions
Fulvestrant	Oncology	ESR1, PGR	Hormone receptor positive	Indications and Usage, Clinical Pharmacology, Clinical Studies
Galantamine	Neurology	CYP2D6	CYP2D6 poor metabolizers	Clinical Pharmacology
Gefitinib	Oncology	EGFR	EGFR exon 19 deletions or exon 21 substitution (L858R) mutation positive	Indications and Usage, Dosage and Administration, Clinical Pharmacology, Clinical Studies
Glimepiride	Endocrinology	G6PD	G6PD deficient	Warnings and Precautions, Adverse Reactions
Glipizide	Endocrinology	G6PD	G6PD deficient	Precautions
Glyburide	Endocrinology	G6PD	G6PD deficient	Precautions
Hydralazine	Cardiology	NAT1-2	NAT 1-2 slow acetylators	Clinical Pharmacology
Ibrutinib	Oncology	del (17p)	Chromosome 17p deletion positive	Indications and Usage, Clinical Studies

Continuance of Table 1.

Iloperidone	Psychiatry	CYP2D6	CYP2D6 poor metabolizers	Dosage and Administration, Warnings and Precautions, Drug Interactions, Clinical Pharmacology
Imatinib (1)	Oncology	KIT	KIT protein expression positive, c-KIT D816V mutation negative	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies
Imatinib (2)	Oncology	BCR-ABL1	Philadelphia chromosome positive	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies
Imatinib (3)	Oncology	PDGFRB	PDGFR gene rearrangement positive	Indications and Usage, Dosage and Administration, Clinical Studies
Imatinib (4)	Oncology	FIP1L1-PDGFRA	FIP1L1-PDGFRα fusion kinase (or CHIC2 deletion) positive	Indications and Usage, Dosage and Administration, Clinical Studies
Imipramine	Psychiatry	CYP2D6	CYP2D6 poor metabolizers	Precautions
Indacaterol	Pulmonary	UGT1A1	UGT1A1*28 allele homozygotes	Clinical Pharmacology
Irinotecan	Oncology	UGT1A1	UGT1A1*28 allele carriers	Dosage and Administration, Warnings and Precautions, Clinical Pharmacology
Ivacaftor	Pulmonary	CFTR	CFTR G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, R117H mutation positive, F508del mutation homozygotes	Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies
Lacosamide	Neurology	CYP2C19	CYP2C19 poor metabolizers	Clinical Pharmacology
Lansoprazole	Gastroenterology	CYP2C19	CYP2C19 intermediate or poor metabolizers	Drug Interactions
Lapatinib (1)	Oncology	ERBB2	HER2 protein overexpression positive	Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies
Lapatinib (2)	Oncology	HLA-DQA1, HLA-DRB1	HLA-DQA1*0201 or HLA-DRB1*0701 allele carriers	Clinical Pharmacology
Lenalidomide	Hematology	del (5q)	Chromosome 5q deletion positive	Boxed Warning, Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Studies
Lesinurad	Rheumatology	CYP2C9	CYP2C9 poor metabolizers	Clinical Pharmacology
Letrozole	Oncology	ESR1, PGR	Hormone receptor positive	Indications and Usage, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Lomitapide	Endocrinology	LDLR	LDL receptor mutation homozygotes	Indication and Usage, Warnings and Precautions, Adverse Reactions, Clinical Studies
Ivacaftor and Lumacaftor	Pulmonary	CFTR	CFTR F508del mutation homozygotes	Indications and Usage, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Mafenide	Infectious Diseases	G6PD	G6PD deficient	Warnings, Adverse Reactions
Mercaptopurine	Oncology	TPMT	TPMT intermediate or poor metabolizers	Clinical Pharmacology, Warnings, Precautions, Adverse Reactions, Dosage and Administration
Methylene Blue	Hematology	G6PD	G6PD deficient	Precautions
Metoclopramide (1)	Gastroenterology	CYB5R1-4	NADH cytochrome b5 reductase deficient	Precautions
Metoclopramide (2)	Gastroenterology	G6PD	G6PD deficient	Precautions
Metoprolol	Cardiology	CYP2D6	CYP2D6 poor metabolizers	Clinical Pharmacology
Mipomersen	Endocrinology	LDLR	LDL receptor mutation heterozygotes and homozygotes	Indications and Usage, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Studies

Continuance of Table 1.

Modafinil	Psychiatry	CYP2D6	CYP2D6 poor metabolizers	Clinical Pharmacology, Precautions
Mycophenolic Acid	Transplantation	HPRT1	HGPRT-deficient	Warnings and Precautions
Nalidixic Acid	Infectious Diseases	G6PD	G6PD deficient	Precautions, Adverse Reactions
Nefazodone	Psychiatry	CYP2D6	CYP2D6 poor metabolizers	Precautions
Nilotinib (1)	Oncology	BCR-ABL1	Philadelphia chromosome positive	Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies
Nilotinib (2)	Oncology	UGT1A1	UGT1A1*28 allele homozygotes	Clinical Pharmacology
Nitrofurantoin	Infectious Diseases	G6PD	G6PD deficient	Warnings, Adverse Reactions
Nivolumab (1)	Oncology	BRAF	BRAF V600 mutation-positive	Indications and Usage, Adverse Reactions, Clinical Studies
Nivolumab (2)	Oncology	CD274	PD-L1 protein expression positive	Clinical Pharmacology
Nortriptyline	Psychiatry	CYP2D6	CYP2D6 poor metabolizers	Precautions
Obinutuzumab	Oncology	MS4A1	CD20 antigen positive	Clinical Studies
Olaparib	Oncology	BRCA1-2	BRCA1-2 mutation positive	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Omacetaxine	Oncology	BCR-ABL1	Philadelphia chromosome positive	Clinical Pharmacology, Clinical Studies
Ombitasvir, Paritaprevir, Ritonavir, and Dasabuvir	Infectious Diseases	IFNL3	IL28B rs12979860 T allele carriers (non-C/C genotype)	Clinical Studies
Omeprazole	Gastroenterology	CYP2C19	CYP2C19 poor metabolizers	Drug Interactions
Osimertinib	Oncology	EGFR	EGFR T790M mutation positive	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Palbociclib (1)	Oncology	ESR1	Estrogen receptor positive	Indications and Usage, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Palbociclib (2)	Oncology	ERBB2	HER2 protein overexpression negative	Indications and Usage, Adverse Reactions, Clinical Studies
Palonosetron	Gastroenterology	CYP2D6	CYP2D6 poor metabolizers	Clinical Pharmacology
Panitumumab (1)	Oncology	EGFR	EGFR protein expression positive	Clinical Pharmacology, Clinical Studies
Panitumumab (2)	Oncology	KRAS	KRAS codon 12 and 13 mutations negative	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Pantoprazole	Gastroenterology	CYP2C19	CYP2C19 poor metabolizers	Clinical Pharmacology
Parathyroid Hormone	Inborn Errors of Metabolism	CASR	Calcium-sensing receptor mutation positive	Indications and Usage, Clinical Studies
Paroxetine	Psychiatry	CYP2D6	CYP2D6 extensive and poor metabolizers	Drug Interactions, Clinical Pharmacology
Pazopanib	Oncology	UGT1A1	UGT1A1*28 allele homozygotes	Clinical Pharmacology, Warnings, and Precautions
PEG-3350, Sodium Sulfate, Sodium Chloride, Potassium Chloride, Sodium Ascorbate, and Ascorbic Acid	Gastroenterology Rheumatology	G6PD G6PD	G6PD deficient G6PD deficient	Warnings and Precautions Contraindications, Patient Counseling Information
Pegloticase				
Pembrolizumab (1)	Oncology	BRAF	BRAF V600 mutation-positive	Indications and Usage, Adverse Reactions, Clinical Studies
Pembrolizumab (2)	Oncology	CD274	PD-L1 protein expression positive	Indications and Usage, Dosage and Administration, Clinical Pharmacology, Clinical Studies

Continuance of Table 1.

Perphenazine	Psychiatry	CYP2D6	CYP2D6 poor metabolizers	Clinical Pharmacology, Precautions
Pertuzumab	Oncology	ERBB2	HER2 protein overexpression positive	Indications and Usage, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Phenytoin (1)	Neurology	CYP2C9	CYP2C9 variant allele carriers	Clinical Pharmacology
Phenytoin (2)	Neurology	CYP2C19	CYP2C19 variant allele carriers	Clinical Pharmacology
Phenytoin (3)	Neurology	HLA-B	HLA-B*1502 allele carriers	Warnings
Pimozide	Psychiatry	CYP2D6	CYP2D6 poor metabolizers	Precautions, Dosage, and Administration
Ponatinib	Oncology	BCR-ABL1	Philadelphia chromosome positive; T315I mutation positive	Indications and Usage, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies
Prasugrel (1)	Cardiology	CYP2C19	CYP2C19 poor metabolizers	Use in Specific Populations, Clinical Pharmacology, Clinical Studies
Prasugrel (2)	Cardiology	CYP2C9	CYP2C9 variant allele carriers	Use in Specific Populations, Clinical Pharmacology, Clinical Studies
Prasugrel (3)	Cardiology	CYP3A5	CYP3A5 variant allele carriers	Use in Specific Populations, Clinical Pharmacology, Clinical Studies
Prasugrel (4)	Cardiology	CYP2B6	CYP2B6 variant allele carriers	Use in Specific Populations, Clinical Pharmacology, Clinical Studies
Pravastatin	Endocrinology	LDLR	LDL receptor mutation heterozygotes and homozygotes	Indications and Usage, Use in Specific Populations, Clinical Studies
Prilocaine and Lidocaine (1)	Anesthesiology	CYB5R1-4	NADH-cytochrome b5 reductase deficient	Warnings and Precautions
Prilocaine and Lidocaine (2)	Anesthesiology	G6PD	G6PD deficient	Warnings and Precautions
Primaquine	Infectious Diseases	G6PD	G6PD deficient	Warnings and Precautions, Adverse Reactions
Propafenone	Cardiology	CYP2D6	CYP2D6 poor metabolizers	Dosage and Administration, Warnings and Precautions, Clinical Pharmacology
Propranolol	Cardiology	CYP2D6	CYP2D6 poor metabolizers	Clinical Pharmacology
Protriptyline	Psychiatry	CYP2D6	CYP2D6 poor metabolizers	Precautions
Quinidine	Cardiology	CYP2D6	CYP2D6 poor metabolizers	Precautions
Quinine Sulfate (1)	Infectious Diseases	G6PD	G6PD deficient	Contraindications
Quinine Sulfate (2)	Infectious Diseases	CYP2D6	CYP2D6 poor metabolizers	Drug Interactions
Rabeprazole	Gastroenterology	CYP2C19	CYP2C19 poor metabolizers	Drug Interactions, Clinical Pharmacology
Rasburicase (1)	Oncology	G6PD	G6PD deficient	Boxed Warning, Contraindications, Warnings and Precautions
Rasburicase (2)	Oncology	CYB5R1-4	NADH-cytochrome b5 reductase deficient	Boxed Warning, Warnings and Precautions
Rifampin, Isoniazid, and Pyrazinamide	Infectious Diseases	NAT1-2	NAT 1-2 slow acetylators	Clinical Pharmacology, Adverse Reactions
Risperidone	Psychiatry	CYP2D6	CYP2D6 poor metabolizers	Clinical Pharmacology
Rituximab	Oncology	MS4A1	CD20 antigen positive	Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies
Rosuvastatin (1)	Endocrinology	SLCO1B1	SLCO1B1 reduced function allele homozygotes	Clinical Pharmacology
Rosuvastatin (2)	Endocrinology	LDLR	LDL receptor mutation heterozygotes and homozygotes	Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies

Continuance of Table 1.

Sevoflurane	Anesthesiology	RYR1	Ryanodine receptor mutation positive	Warnings
Simeprevir	Infectious Diseases	IFNL3	IL28B rs12979860 T allele carriers (non-C/C genotype)	Clinical Pharmacology, Clinical Studies
Sodium Nitrite	Toxicology	G6PD	G6PD deficient	Warnings and Precautions
Sodium Phenylacetate and Sodium Benzoate	Inborn Errors of Metabolism	NAGS, CPS1, ASS1, OTC, ASL, ABL2	Urea cycle enzyme deficient	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Drug Interactions, Use in Specific Populations, Overdosage, Clinical Pharmacology, Clinical Studies
Sofosbuvir	Infectious Diseases	IFNL3	IL28B rs12979860 T allele carriers (non-C/C genotype)	Clinical Studies
Succimer	Hematology	G6PD	G6PD deficient	Clinical Pharmacology
Sulfamethoxazole and Trimethoprim	Infectious Diseases	G6PD	G6PD deficient	Precautions
Tamoxifen (1)	Oncology	ESR1, PGR	Hormone receptor positive	Clinical Pharmacology, Indications and Usage, Precautions, Adverse Reactions
Tamoxifen (2)	Oncology	F5	Factor V Leiden carriers	Warnings
Tamoxifen (3)	Oncology	F2	Prothrombin G20210A allele positive	Warnings
Telaprevir	Infectious Diseases	IFNL3	IL28B rs12979860 T allele carriers (C/T and T/T genotype)	Clinical Pharmacology, Clinical Studies
Tetrabenazine	Neurology	CYP2D6	CYP2D6 poor metabolizers	Dosage and Administration, Warnings and Precautions, Use in Specific Populations, Clinical Pharmacology
Thioguanine	Oncology	TPMT	TPMT intermediate or poor metabolizers	Warnings, Precautions, Dosage and Administration
Thioridazine	Psychiatry	CYP2D6	CYP2D6 poor metabolizers	Contraindications, Warnings, Precautions
Ticagrelor	Cardiology	CYP2C19	CYP2C19 poor metabolizers	Clinical Studies
Tolterodine	Urology	CYP2D6	CYP2D6 poor metabolizers	Warnings and Precautions, Drug Interactions, Use in Specific Populations, Clinical Pharmacology
Tositumomab	Oncology	MS4A1	CD20 antigen positive	Indications and Usage, Clinical Pharmacology
Tramadol	Anesthesiology	CYP2D6	CYP2D6 poor metabolizers	Clinical Pharmacology
Trametinib	Oncology	BRAF	BRAF V600E/K mutation-positive	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Pharmacology, Clinical Studies, Patient Counseling Information
Trastuzumab	Oncology	ERBB2	HER2 protein overexpression or gene amplification positive	Indications and Usage, Warnings and Precautions, Clinical Pharmacology, Clinical Studies
Tretinoin	Oncology	PML-RARA	PML-RARα translocation positive	Clinical Pharmacology, Indications and Usage, Warnings
Trimipramine	Psychiatry	CYP2D6	CYP2D6 poor metabolizers	Precautions
Valproic Acid (1)	Neurology	POLG	POLG mutation positive	Boxed Warning, Contraindications, Warnings and Precautions
Valproic Acid (2)	Neurology	NAGS, CPS1, ASS1, OTC, ASL, ABL2	Urea cycle enzyme deficient	Contraindications, Warnings, and Precautions
Vemurafenib (1)	Oncology	BRAF	BRAF V600E mutation-positive	Indications and Usage, Dosage and Administration, Warnings and Precautions, Clinical Pharmacology, Clinical Studies, Patient Counseling Information
Vemurafenib (2)	Oncology	NRAS	NRAS mutation positive	Warnings and Precautions, Adverse Reactions
Venlafaxine	Psychiatry	CYP2D6	CYP2D6 poor metabolizers	Precautions
Voriconazole	Infectious Diseases	CYP2C19	CYP2C19 intermediate or poor metabolizers	Clinical Pharmacology
Vortioxetine	Psychiatry	CYP2D6	CYP2D6 poor metabolizers	Dosage and Administration, Clinical Pharmacology

Continiance of Table 1.

Warfarin (1)	Hematology	CYP2C9	CYP2C9 intermediate or poor metabolizers	Dosage and Administration, Drug Interactions, Clinical Pharmacology
Warfarin (2)	Hematology	VKORC1	VKORC1 rs9923231 An allele carriers	Dosage and Administration, Clinical Pharmacology
Warfarin (3)	Hematology	PROS1	Protein S deficient	Warnings and Precautions
Warfarin (4)	Hematology	PROC	Protein C deficient	Warnings and Precautions

Research and development strategy in pharmaceutical industry for personalized medicine

The advantage of the molecular foundation of sickness is already reworking pharmaceutical development. Drug discovery and development has usually been a linear system (Figure 3) with little suggestions from later medical development levels on the overall approach. The adoption of a PM approach in drug discovery and development necessitates a paradigm shift from a linear method to a heuristic one (Figure 4).

Figure 3. Typical drug discovery – a linear procedure. The historic procedure of drug discovery has been linear, with little opportunity for feedback or development on the upstream add-ons of the system from downstream results Abbreviations: FDA, meals and Drug Administration; HTS, excessive-throughput screening (ref. (39) with permission)

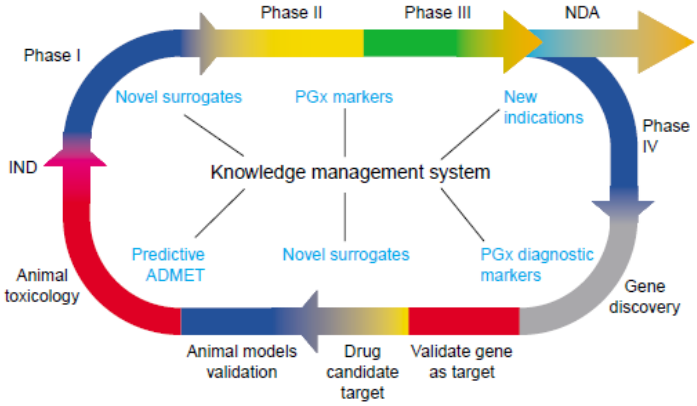

Figure 4. Future drug discovery an integrated method. Genomic expertise and markers rising at each stage of the discovery process will probably be used as tools each upstream and downstream, resulting in higher prescription drugs and PM merchandise A talents warehouse will retailer understanding enabling continued approach and product improvements Abbreviations: ADMET, absorption, distribution, metabolism, excretion and toxicity, IND, investigational new drug; NDA, new drug application (ref. (39) with permission).

This new method will involve a series of study feedback loops. The early stages of discovery, together with decision and validation of drug ambitions, small-molecule screening and chemistry, and preclinical comparison of compounds, will probably be linked with later phases of medical progress. Molecular, pharmacological and sufferer scientific knowledge will be captured at quite a lot of phases and integrated into a 'knowledge management system' that will be used to facilitate rational drug design round molecular ailments.

Genomic technologies have already taken preserve and are impacting the pharmaceutical industry. Excessive throughput sequencing and transcript profiling had been utilized to cell-founded and animal units of disease or instantly to human tissues to identify speedily gene ambitions that initiate the drug discovery procedure. Bioinformatics, proteomics and animal models are used to additional validate genes as goals before proceeding to high-throughput screening of giant compound libraries for the progress of small-molecule medications. The have an effect on of genomics on drug development can already be noticeable: Millennium prescribed drugs (Cambridge,

MA) and Bayer AG (Leverkusen, Germany) introduced what is believed to be the primary small molecule drug candidate found out against a genomics-derived goal in the discipline of melanoma (40). In the near future, a flood of new drug treatments distinct at the molecular basis of sickness will grow to be available.

Genomic technologies applied to goal identification can concurrently establish genes which can be co-regulated with drug targets. Each objective and co-regulated genes might be talents displace biomarkers for use in preclinical and medical stories, an example of the integration of the early and late stages of drug discovery and progress. Ultimate displaces markers include cellphone-surface proteins and secreted proteins, that are amenable to touchy mass-spectroscopic or antibody founded detection in the blood. The gene encoding leptin, a regulator of physique fat, discovered making use of genomic applied sciences (17), is not only validated to be a valuable drug target however blood leptin phases probably of use as a monitoring marker of drug-related weight achieve (41) or as a response to growth hormone therapy in youngsters (41). Extra down the invention method, toxicogenomic markers predictive for adversarial drug reactions (ADRs) could impact the resolution and optimization of lead compounds before human studies. Microarray analytical tools to outline molecular profiles that predict ADRs in humans are being investigated using present hepatotoxicity, nephrotoxicity, cardiotoxicity or bone marrow suppression. Businesses similar to Affymetrix (Santa Clara, CA), Gene good judgment (Gaithersburg, MD) and Curagen (New Haven, CT) are constructing gene expression-centered assays that can be utilized to test preclinical compounds for their propensity to induce ADRs based on these reviews. Pharmacodynamics and Pharmacogenomics markers predictive of drug toxicity in humans can be introduced in phase I, II or III scientific trials were, in principle, sufferer determination and/or stratification within reviews will also be guided on the basis of markers correlating with safety and efficacy. Contemporary reports of human genetic version within the cytochrome P450 (CYP) enzymes which are largely liable for drug metabolism, for illustration, have steered that making use of a person genetic variant at these loci to prefer patients for clinical trials would shrink ADRs by means of 10%–20% (42).

Pharmacogenomics might be predominant aspect of PM and is already being embraced by using pharmaceutical corporations as a means of bettering effectivity within the drug development method. An individual's response to a drug is the intricate combo of each genetic and non-genetic reason. Genetic editions within the drug goal itself, disease pathway genes or drug-metabolizing enzymes, would all be used as predictors of drug efficacy or toxicity. The pharmaceutical enterprise has well-known the a priori want for tools to enable pharmacogenomics research. In 1999, ten companies and the Wellcome trust fashioned a consortium to realize and map essentially the most original style of genetic variation, single nucleotide polymorphisms (SNPs). To this point, >800 000 SNPs had been deposited into the SNP Consortium's public database (http://www.Snp.Cshl.Org). A high-decision SNP map will expedite the identification of genes for intricate illnesses, akin to asthma, diabetes mellitus, atherosclerosis and psychiatric issues. The SNP database may also be a device for pharmacogenomics investigations for the period of medical development. In these days, many pharmaceutical firms are designing their clinical trials to enable the movement's collection and storage of DNA and different biological specimens in order to be utilized in future pharmacogenomics reports. Careful biological monitoring throughout scientific development will not best lead to pharmacogenomics markers that accompany the drug available on the market but also will have enough money possibilities to use human organic know-how to previous phases of discovery and progress. Molecular profiles of patients recognized in the segment I and II scientific experiences as likely non-responders (probably indicating tricky molecular taxonomy of the ailment being treated) might symbolize an opportunity for pharmaceutical companies to provoke discovery packages. Novel therapies would be developed across the non-responders' specified molecular subtype of the disease. The PM process for drug discovery and development will have to yield a spectrum of product opportunities for the pharmaceutical industry. Diagnostic danger evaluation and disorder-monitoring tools that effectively quantify disorder burden in patients can be an instantaneous end result of study for the duration of the early discovery approach. Pharmacogenomics markers of efficacy and aspect effects will likely be used along with unique medications to goal drug medication to these patients who could have an ideal response. The business purpose for precise healing procedures, which some argue will scale down market share, is that such products will eventually increase the market by using recruiting sufferers from less strong treatment plans or by using making a choice on much less symptomatic contributors who would improvement from the prophylactic remedy. The clinical phases of drug progress afford the opportunity to seize sufferer medical data, imaging and in vitro molecular response knowledge simultaneously (39).

Academic medical centers and clinical research organizations are now conducting clinical trials with future study in mind. Archiving organic specimens along with usual scientific covariates is becoming hobbies. Some facilities are additionally actively engaged in pharmacogenomics market research. In the near future, scientific trials probably conducted in specialized items the place specified medical, organic and genomic knowledge are accrued and integrated. Genome- and proteome-vast profiles in conjunction with organic pathway databases, imaging and medical information on each patient shall be used to research an individual's ailment and drug response. The understanding of the biology of sickness and drug motion gleaned from these sophisticated new paradigms will dramatically accelerate the cognizance of truly PM (39).

Conclusion

PM promises the chance to benefit from probably the most powerful therapy that goals of sickness, keeping off toxicity (drug safeguard) for sufferers and for payers it's attractive as a mechanism to make the application of steeply-priced drugs, and preclude useless highly-priced on treatments which can be useless. Alternatively, for the pharmaceutical industry PM offers both challenge and opportunities. Many pharmaceutical corporations have dedicated to the imaginative and prescient of 'right drug, proper sufferer, correct time, especially in therapeutic areas comparable to oncology and neuroscience. Pharma knows that this approach supplies the risk to gain terrific medical advances in exact sufferer populations, compared with presently available "non-particular" medicinal drugs. Drug progress timelines could be accelerated, and success premiums expanded with the aid of doing trials in molecularly selected patient populations those outcomes in additional rapid proof of notion and more mighty clinical effects, allowing smaller phase III assessments. However, there are additionally gigantic challenges. Most significantly, the drug developer ought to be in a position to reach the desired return on funding despite the restricted market size and drug progress bills is also expanded because of the complexities of biomarker evaluation and diagnostic progress. Molecular profiling is an emerging science and various pleasant and pricey drug progress applications have faltered due to the alternative of the flawed biomarker to guide sufferer choice. Trials involving biomarkers are attracting high curiosity from researchers, but require new potential in trial design, information evaluation and investigator competencies in pattern assortment and administration (switching from a linear approach to a heuristic one). World regulatory approaches for partner diagnostics are nonetheless more diverse and challenging. Moreover, the companion diagnostic needs to be available for validation for the period of the medical development segment, but with the hazards inherent in drug progress, and restrained repayment, diagnostic producers have little incentive to boost such checks "at chance." Despite the challenges, personalized medication is largely believed to present the satisfactory prospect of mighty healing and therapy for patients with critical illnesses. The crucial stakeholders-Pharma and biotech, diagnostic organizations, regulatory businesses, payers and policy makers, ought to be dedicated to exercising together to furnish incentives and put off obstacles so that this intention can turn out to be a fact.

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