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## Omics Screening for Pharmaceutical Efficacy and Safety in Clinical Practice

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### Abstract

As molecular techniques have improved, investigators have attempted to improve pharmaceutical efficacy and safety by making trait associations with genomic, epigenomic, transcriptomic, proteomic, and metabolomic polymorphisms. The ‘omics era has seen screening assays for pharmaceutical efficacy and safety translated into clinical practice. This manuscript will discuss each ‘omic field and the screening assays available to the clinician. While success has been demonstrated in each ‘omic field, many challenges remain. Assays need wider availability, predictive values remain low, and costs remain high. In order for clinicians to realize improved efficacy and safety due ‘omic screens, development of improved techniques, combining of ‘omic assays, and increased clinical utilization is necessary. This is an exciting time for investigators and clinicians that desire improved pharmaceutical therapy.

### Introduction

The Human Genome Project (HGP) spawned an eruption of research focused on achieving personalized medicine. Clinicians and researchers hoped that sequencing of the human genome would allow for prediction of disease and personalized pharmaceutical therapy based on an individual’s genetic polymorphisms. Quickly researchers realized the limitations of simple genome associations in clinical medicine. The positive and negative predictive values of genome associations have been poor largely making them ineffective for clinical screening, thus researchers have turned to the downstream products of the genetic sequence. Epigenomics, transcriptomics, proteomics, and metabolomics are fields born out of both the increased knowledge as well as the failures of genomics in clinical medicine. The “omics era” has been characterized by a proliferation in translational research to identify markers of disease and factors associated with pharmaceutical efficacy and toxicity. There are an incredible number of ‘omics investigations relating to a myriad of human diseases; a comprehensive review of the available screens for human disease is impractical. The objective of this manuscript is to review the existing screening tests related to pharmaceutical therapies in each ‘omic category. We will progress through the relevant pharmaceutical screens from the underlying genetic code to ultimate clinical phenotype

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(Figure 1). Inevitably, there will be reference to ‘omic screening in human disease since disease and therapy are irreconcilably entangled.

## Genomics

Genomics is the study of the human genome and the accompanying variability of the contained DNA. Pharmacogenomics, by extension, is the study of how pharmaceutical agents interact with the output of the human genome. In 1956, Arno Motulsky proposed genetic variation as an explanation for individual differences in drug efficacies and adverse reactions. The first pharmacogenomic association was demonstrated with the association of peripheral neuropathy in isoniazid “slow acetylators” in 1960 [1]. Other early genetic associations were largely theoretical until molecular genotyping techniques allowed for a more firm genetic-toxicity linkage. This early neurotoxic-isoniazid association was later confirmed with molecular genotyping techniques. Isoniazid is primarily metabolized by N-acetylation. “Slow acetylators” shunt isoniazid through an alternative CYP isoenzyme to form isonicotinic acid, a neurotoxin that is typically produced in only small amounts by “rapid acetylators” [2].

After the first draft of the HGP was published in 2001 [3], investigators analyzed the genome for common polymorphisms in an attempt to make associations with specific traits within the population. The HapMap Project seeks to catalog common genetic variants describing where the variation occurs within the genome and in which populations worldwide [4,5]. The 1000 Genomes Project seeks to produce an extensive deep catalog of human genetic variation, structural variants, and their haplotype contexts [6]. These projects provide resources for investigators to make large-scale genome level associations. These “genome wide association” (GWA) studies require extremely large sample sizes to reach statistical significance [7]. GWA studies have attempted to provide screening tests for medication-induced toxicity. We have moved from larger gene segment analyses to single base-pair associations using GWA studies. Now single nucleotide polymorphism (SNP) studies seek to characterize functional differences in similar gene outputs putting an even finer point on the genetic polymorphisms within the human population.

## Genomic Screens

Microarray assays are the preferred methodology for genotyping analyses because they allow for screening for a large number of polymorphisms with a small sample of blood without the need for multiple DNA extractions and amplification steps, which increase the potential for error. The DNA is isolated, digested, labeled then hybridized within a microarray-well containing the oligonucleotide sequences of interest. Commercial laboratories and pharmaceutical companies now offer United States Food and Drug Association (US FDA) approved screening assays to evaluate for a range of pharmaceutical efficacy and safety (Table 1).

Genomic screening has become standard of care for many oncologic therapies. Genomics has been researched and utilized most extensively in this field due to the frequency of patient enrollment in clinical trials and the wide availability of tissue samples for genetic analysis. Tumor genetic polymorphisms have been associated with improved efficacy, identification of resistance, and toxicity of cancer therapeutics. The National Comprehensive Cancer Network (NCCN) now recommends screens for tumor specific genes associated with better chemotherapeutic efficacy [8]. Examples include human epidermal growth receptor 2 (HER2) screening in breast cancer [9,10] and gastric cancer [11] which dictates response to the specific immunologic adjuvant therapy trastuzumab. Optimal testing for HER2 remains controversial and both genomic (fluorescence in situ hybridization [FISH]) and proteomic screens (immunohistochemistry [IHC]) are available though the tests should be used in

concert [12]. Cetuximab therapy in metastatic colon cancer is associated with a favorable cost-benefit analysis in tumors with the KRAS wild type gene [13] and KRAS mutations have been associated with a failure of the epidermal growth factor receptor tyrosine kinase inhibitors erlotinib and gefitinib in non-small cell lung cancer [14]. BRAF mutations have been associated with failure of therapy in colorectal cancers [15] and improved survival in melanoma patients receiving vemurafenib [16]. See Table 2 for a list of 'omics screens available for oncology pharmaceuticals.

One of the most commonly utilized genomic screens in pharmaceutical prescribing is HLA-B\*5701 screening for abacavir hypersensitivity. This is likely due to clinical trial data demonstrating improved patient outcomes [17] and the overall prevalence of HIV-1 infection in the population yielding ample opportunity for testing. Interestingly, the positive predictive value (PPV) of this screen was only 47.9% yet the test has become standard of care in Infectious Disease clinics.

Significant effort has been invested in genomic screening for warfarin dosing. Several large studies have demonstrated decreased dosing variability [18], decreased hospitalization [19], and earlier time to stable dosing [20]. Demographic and environmental factors have been added to known genotype associations in an effort to further improve efficacy and safety. An unvalidated algorithm including integration of multiple genetic polymorphisms is available to clinicians at [www.warfarindosing.org](http://www.warfarindosing.org) [21]. However, even with incorporation of multiple factors, only 40% of the variability in response to warfarin can be predicted.

It is estimated that more than 90% of known drugs are metabolized by hepatic cytochromes (CYPs) 1A2, 2C9, 2C19, 2D6, 2E1, and 3A4 [22] thus genetic polymorphism in these enzymes is likely to play a large role in drug response. CYP screening is available though application to clinical practice has yet to be regularly employed by clinicians. This is likely due to multiple factors including inherent redundancy in the metabolic function of the CYP enzymes, variable penetrance (expressed phenotype predicted by genotype) [23,24], and lack of clinical data to demonstrate improved patient outcomes. Clinicians, however, should be aware of these screens because polymorphism has been associated with alteration in both clinical efficacy [25,26] and toxicity [27].

The best studied of these enzymes is CYP2D6. It metabolizes approximately 25% of known medications including antidepressants, antipsychotics, anti-arrhythmics,  $\beta$ -blockers, and analgesics. Toxicity and lack of efficacy have been demonstrated due to variable CYP2D6 gene expression [28,29]. However, CYP2D6 screening prior to initiation of therapy is not currently recommended prior to initiation of CYP2D6 dependent medications. CYP2C19 screening has recently been shown to be associated with variable pharmacodynamic responses to clopidogrel [25] and improved outcomes after percutaneous coronary intervention [30]. Again, screening prior to therapy is not currently recommended by major clinical societies though currently underway trials attempting to demonstrate improved outcomes may soon change this. Polymorphisms in other CYP enzymes have been associated with alterations in medication pharmacokinetics and pharmacodynamics subsequently leading to alterations in clinical efficacy and safety [31,32]. However, these associations suffer from the same limitations as other genomic screens, primarily low positive predictive values and failure to demonstrate improved outcomes. While a range of pharmacogenomic screens are available, physicians must realize their limitations in clinical practice.

## Limitations of Genomic Screens

Pharmacogenomic screens have become more available with the publication of the human genome sequence and the resulting proliferation of laboratories specialized in

characterization of its variation. There are few FDA approved genomic screens available (Table 1) though local laboratories can provide sequencing and analysis in their respective areas of specialty.

Cost remains a major barrier to wide adoption of pharmacogenomic screening. A genomic screen may cost a patient anywhere between \$100 to several thousand dollars depending upon the number of polymorphisms sought, and the vendor pricing. Single screens have become less expensive with commercialization, utilization of microarray techniques, and increased clinical demand. For instance the HLA-B\*5701 screen for abacavir hypersensitivity can be obtained for approximately \$150 in patient cost.

Insurance company re-imburement remains a limitation to utilization in clinical practice. Perhaps recent trials demonstrating pharmacodynamic associations with genomic polymorphisms [19,20,25] will lead to an investment in screening algorithms that will ultimately decrease clinical costs. However, re-imburement is unlikely to change until clinical trials demonstrate improved outcomes with antecedent pharmacogenomic screening.

The positive and negative predictive values of currently available screening tests remain the major limitation of these assays. Combining polymorphism screening for CYP2C19 and the vitamin K epoxide reductase complex (VKORC1) only resulted in 41% prediction of the variability in warfarin doses [18]. This combination screen represents the most effective pharmacogenomic screen to date and highlights the shortcomings of utilizing genomics alone. The abacavir and warfarin screens represent the most successful efforts toward “individualized medicine” thus far. The two approaches highlight fundamental differences in screening needs. In one case, toxicity is avoided by identification of one specific polymorphism. In the other case, multiple factors are integrated to improve efficacy. Both situations have yielded less than a 50% success rate for prediction of safety and efficacy [17,18]. This suggests other factors contribute to the ultimately observed phenotype. This has prompted research into the downstream ‘omic fields.

## Epigenomics

The term epigenomics refers to environmental factors that regulate gene expression but are not inherently part of the genome. These factors include DNA methylation, variations in histone wrapping, RNA silencing, among other factors. Epigenomic factors are major determinants of when and whether genes are expressed. This field has potential to account for differences in gene expression in different populations and geographic regions affecting drug response from the same genetic code. Numerous methods have been used for analysis of epigenetic factors in basic science laboratories and technique optimization is still underway [33].

## Epigenomic Screens

Identification of environmental exposures associated with epigenetic changes leading to cancer [34] is a ripe area of investigation. Expansion into a greater number of human disease processes occurs monthly. The bulk of pharmacoepigenetic work has been done in chemotherapeutic agents. For instance, hypomethylation of the multi-drug resistance gene 1 (MDR-1) dictates increased expression of the gene in the setting of daunorubicin and etoposide treatment [35]. Epigenetic factors have been shown to affect the expression of numerous CYP genes [36] and characterization may account for variation in functionality in patients with the same underlying genetic code. Few other pharmaceutical related epigenetic screens have been investigated.

## Limitations of Epigenomic Screens

The major clinical limitation of this field is availability. Ultimately, epigenetic screens validated in one population will be difficult to apply globally due to the inherent differences in environmental factors between populations. This may limit the generalizability of epigenetic screens across populations.

## Transcriptomics

Transcriptomics is defined as the study of how the human genome is expressed. Changes in epigenomic, local cellular environment and expression of other genes can alter the human “transcriptome”. The true clinical utility of transcriptomic screens lies in their potential to characterize organ biology through biomarkers in the blood. For example, a medication may modify gene transcription in the liver. The mRNA or miRNA profile released from hepatocytes can be measured in serum [37] and the changes can be used to measure the response to treatment. Additionally, peripheral blood cells may change their transcripts in response to a therapy. The measurement of these transcript biomarkers in plasma may provide a means to detect organ specific biologic changes without the need to examine the organ tissue itself, which limits pharmacogenomic and pharmacoepigenomic screens.

## Transcriptomic Screens

The most clinically utilized multi-gene transcriptomic screen is the AlloMap (XDx, Inc.), which screens for 11 gene expression levels associated with cardiac transplant rejection. This screen minimizes the need for endomyocardial biopsy in cardiac transplant patients [38] and is now covered by most health insurance companies. This screen is not a direct marker of pharmaceutical efficacy or toxicity but rather, a test for expression of genes associated with rejection that may prompt clinicians to alter pharmaceutical therapy. Two breast cancer multi-gene expression assays are available, the Oncotype DX (Genomic Health, Inc., CA, USA) which screens for tumor expression of 21 genes [39] and the MammaPrint (Agendia, Amsterdam, The Netherlands) which screens for expression of 70 tumor genes [40]. These screens require tissue of resected or biopsied tumors. Several chronic myeloid leukemia (CML) mutations have been associated with varying efficacy of chemotherapeutics [41]. The NCCN now recommends following BCR-ABL kinase transcript levels throughout therapy and consider significant changes an indication to change therapy [42]. Estrogen receptor/progesterone receptor (ER/PR) testing is recommended at diagnosis of all breast cancers to determine appropriate adjuvant chemotherapy. Classically, this testing is performed using immunohistochemistry (IHC) techniques on resected/biopsied tissue though peripheral sampling followed by RT-PCR is becoming more reliable and clinically available [43,44].

## Limitations of Transcriptomic Screens

Transcriptomic analyses have largely failed to move into the clinical arena to date. This field remains entrenched in basic science laboratories with few efforts to move the technique into translational studies. The fundamental limitation of using transcriptomic assays is that mRNAs are intermediate products of disease that fail to adequately predict the clinical effect. Polymorphism of downstream proteins including post-translational changes, changes in second-messenger systems, and interaction with downstream metabolic enzymes leads to persistent variability of the observed clinical effect. This is compounded by short mRNA half-lives resulting in difficulty in quantitative interpretation [45]. Circulating cancer cells may represent a biologically distinct cell type when compared to the primary tumor transcriptome. This discordance has been observed in circulating breast cancer transcription of ER/PR [46]. Biomarkers have been studied in numerous animal models and when applied

in humans, they have not performed better than a coin-flip for prediction of disease/toxicity. Perhaps continued work that characterizes the kinetics of mRNAs/transcripts and further enhancement of sensitivity of their detection will lead to a larger role of transcriptomic analysis in pharmacotherapy.

## Proteomics

In the same Nature issue that published the first draft of the HGP [3], The Human Proteome Organization (HUPO) announced their efforts to increase resources for characterization of the proteins encoded by the HGP [47]. Proteomics is defined as the study of proteins and their variability in human disease states. The proteome may vary between different individuals, different organs, or even between cells in the same organ in an individual. Most efforts have focused upon characterizing protein mediators and predictors of disease rather than the protein targets of pharmacotherapy.

## Proteomic Screens

The most prominently available proteomic screens are utilized in tumor specific cancer screening. For instance, evaluation of estrogen receptor (ER), and progesterone receptor (PR), is recommended in addition to genomic screening of HER2 for evaluation of newly diagnosed breast cancers. These evaluations are pathology based and are typically performed using IHC assays. IHC may technically be considered a proteomic approach because it quantifies a human protein associated with disease though many would consider it a more traditional pathologic technique because it does not characterize the inherent protein variability. Newer ultrasensitive proteomic techniques use a combination of high performance chromatography and mass spectrometry to characterize thousands of proteins from as little as a microgram of tissue [48]. Identification of a variable proteomic fingerprint has been associated with aspirin resistance and the use of clopidogrel in this population is recommended [49]. Proteomic measurements of inflammatory markers, such as tumor necrosis factor alpha (TNF- $\alpha$ ) and haptoglobin alpha-2-polypeptide has been associated with increased manifestations of atherosclerotic disease in patients with systemic lupus erythematosus (SLE) [50]. Inflammatory markers can be measured by commercial laboratories [51,52] and some have suggested targeting therapies, such as infliximab, in SLE patients with elevated markers [53]. While these tests have face validity, there are no data to demonstrate that therapy modification based on the testing improves patient outcomes.

## Limitations of Proteomic Screens

The major limitation of proteomic screens is that they are tissue specific and therefore require tissue to characterize protein variability. Unlike blood-based targets or resected tumor tissue, from which the pertinent biologic matrix is practical to obtain, tissue samples from organs such as lung, kidney, heart, or brain are not easily obtained for proteomic screens. Most proteomic screens are not yet commercially available to clinicians. While a subset of patients may be able to finance tests such as TNF- $\alpha$ , which costs only a few hundred dollars, no proteomic screens are reimbursed by insurance companies in the United States.

## Metabolomics

Metabolomics is an emerging field that quantitates endogenous and exogenous metabolic products to measure metabolic response or predict disease. Advances in metabolomic techniques have yielded a sensitive approach that may be altered by minute-to-minute physiologic changes and account for upstream variations in an individual's genome, transcriptome, and proteome. Multiple techniques are employed to measure these small



molecule metabolites; a combination of ultra performance liquid chromatography with nuclear magnetic resonance (NMR), orthogonal quadrupole time-of-flight (QTOF), or mass spectroscopy time-of-flight (MALDI TOF) have become the most common and preferred methodologies [54,55], though optimization is still occurring [56]. This approach has been applied to multiple disease processes [57–62]. This approach may ultimately prove to be the most sensitive screening modality for pharmaceutical efficacy and safety in the individual patient because it accounts for upstream genomic, epigenomic, transcriptomic and proteomic factors[63].

## Metabolomic Screens

The classic metabolomic screen for toxicity is for glucose-6-phosphate deficiency (G6PD). G6PD has been associated with xenobiotic-induced hemolysis. The screen can be performed either qualitatively or quantitatively via spectrophotometric metabolite quantification [64]. G6PD testing is used prior to prescription of many anti-malarial therapies and prior to dapsona prescription. G6PD testing is recommended by the Association of Infectious Diseases Society of America for all HIV patients [65]. G6PD status is tested in all US military recruits.

To date, only one clinical trial has demonstrated an ultrasensitive metabolomic relationship between a medication and drug induced liver injury (DILI). The SPORTIF trial examined ximelagatran anticoagulation for stroke prevention in patients with atrial fibrillation. Blood sampling before and after ximelagatran administration revealed that lower levels of serum pyruvate before dosing predicted DILI [66].

Winnike examined the metabolomic profiles of subjects taking therapeutic doses of acetaminophen using NMR spectroscopy and was able to identify evidence of hepatotoxicity suggesting the utility of “early-intervention pharmacometabonomics” [67]. However these evoked metabolomic profiles can’t truly be considered screening tests. This same group demonstrated alterations in acetaminophen urinary metabolite profile predicted by predose p-cresol urinary concentrations [68]. While this study did not directly demonstrate toxicity, it demonstrated proof that screening metabolomic profiles can predict variation in individual metabolic activity, and likely toxicity. Markers of hepatotoxicity have been observed in children taking valproic acid utilizing organic acid metabolism as the metabolic matrix [69]. A similar association has been demonstrated with statin induced liver/muscle toxicity [70]. None of these assays are validated for screening prior to therapy. However, these association studies represent with groundwork required for metabolomic toxicity screening.

Metabolomic profiles have been utilized in drug discovery using small compounds to target specific metabolic changes in specific cell lines [71–73]. This technique suggests that screening of individual metabolomes could predict subsequent pharmaceutical response and may yield more specific therapies.

## Limitations of Metabolomic Screens

At this time, high sensitivity metabolomic screens for pharmacotherapy have not left research laboratories and thus are of little utility to the practicing clinician. The human metabolome needs to be further characterized and subsequently therapeutic associations can be made. In addition, these highly specific techniques raise issues with reproducibility [74]. It is unclear how clinicians will use this sensitive data since even small changes in physiology, such as food ingestion [75] or going up a flight of stairs, can have significant impact on the metabolome [55]. Combining pharmacometabonomics with pharmacogenomics can lead to identification of more clinically relevant associations

[76,77]. If clinicians initially focus on larger stable metabolic signals, such as the output of CYP systems, hopefully we can minimize being misled by transient metabolic associations that do not represent causation.

## The Future 'Omics in Pharmacotherapy

'Omic modalities have utility in screening for efficacy and safety of pharmaceutical therapy. Screening must ultimately fulfill practical criteria in order to be clinically useful. For screening assays that seek to improve efficacy, the positive predictive value (PPV) must be high or patients that may have benefit from the therapy will be inappropriately excluded. Likewise, if a screen is meant to eliminate high morbidity toxicity, such as Stevens-Johnson Syndrome, then the PPV is less important and the negative predictive value (NPV) is more pertinent because false negative screens put patients at significant risk. Predictive values are preferred for clinical screening assays because they account for disease prevalence in the population, which sensitivity and specificity do not. Ideally, the screen would have both high PPV and NPV. However this is unlikely in a single screen due to the limitations listed in the respective 'omic sections. Genomic screens are perfectly suited for rare, high morbidity condition, such as HLA-B\*1502 associated Stevens-Johnson Syndrome in carbamazepine therapy [78]. More common and less severe toxicities, such as statin-rhabdomyolysis, may be best screened by a combination or syllogistic approach. A biologic systems panel (BSP) [79] has the potential to account for several common genetic polymorphisms, proteomic, and metabolomic variables improving the overall predictive values of the panel. More common toxicities may be cost-effectively screened with an initial genomic screen, followed by a functional screen, if positive on the initial screen, so that patients are not denied therapies due to false positive tests.

The complexity of human-medication interactions are further complicated by idiosyncrasies of disease. For instance, HER2 status of breast cancer may change during therapy [80]. The chemotherapeutic agent tamoxifen is metabolically activated by CYP2D6 and despite numerous pharmacokinetic studies demonstrating a lower metabolite serum concentrations [81, 82], no increased rate of breast cancer recurrence in patients taking CYP2D6 inhibitors when compared to controls [83]. This suggests that lower serum concentrations of tamoxifen's active metabolite are sufficient for treatment, or other factors such as tumor specific changes diminish the pharmacokinetic association. Associating metabolic traits with GWA identified genotypes has been shown to improve the predictive value for observed clinical effect for common medical conditions [76,77]. This work highlights the power of combining 'omic methodologies. Again, integration of the 'omics fields into panels may improve the predictive efficacy and safety of prescribing practices.

## Conclusions

'Omics pharmaceutical screens are slowly entering clinical medicine. Continued basic research is necessary to establish a robust matrix of 'omics data. As associations are identified, researchers should determine if pre- therapy screening improves patient outcomes. Insurance companies must be pushed to cover screening assays that enhance outcomes. Integration of numerous 'omics techniques into panels will yield screens with higher positive and negative predictive values. 'Omics panels will prove more clinically useful to physicians than single 'omic screens.

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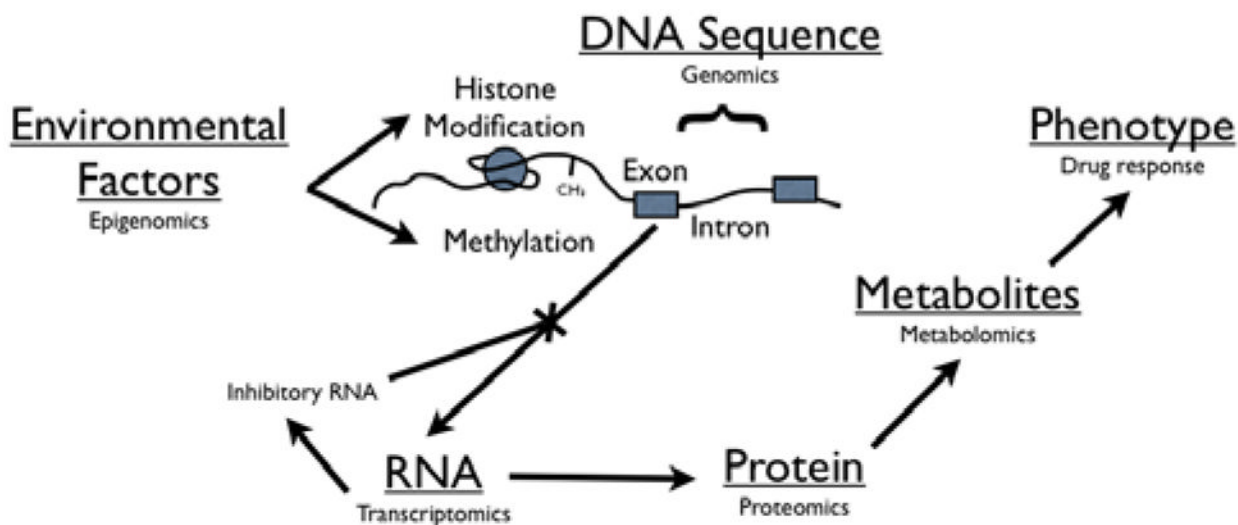
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**Figure 1. Schematic flow from genetic code to drug response**

The study of the inherent genetic code is termed “genomics”. The genome can be modified by environmental factors and study of these factors is termed “epigenomics”. Translation of the genome can be modified by RNA factors and study of the interplay and output of these factors is called “transcriptomics”. Characterization of the subsequent protein output is called “proteomics”. “Metabolomics” is the study of the small molecules that are the product of the above biologic functions. Ultimately these biologic interactions result in the phenotypic trait observed as drug response.

Table 1

FDA approved/recommended screening assays.

Screening Test	Polymorphisms Represented	Pertinent Pharmaceuticals Represented	Limitations
<b>Roche CYP2D6/2C19 AmpliChip®</b>	33 CYP2D6 and 2 CYP19 distinct alleles	25% of known pharmaceuticals[28].	Only represents 25% of known CYP2D6 and only 5.5% of known CYP2C19 polymorphisms.
<b>Affymetrix Drug Metabolizing Enzyme and Transporters (DMET)</b>	225 genes involved in drug absorption, distribution, metabolism, and elimination.	Virtually all pharmaceuticals may be affected by polymorphisms one of these enzymes.	It is unclear how to clinically interpret this matrix output.
<b>HLA-B 5701</b>	HLA-B*5701	Presence of this polymorphism is associated with 47% PPV and 99% NPV of Abacavir hypersensitivity[17]	Poor PPV (due to low prevalence of polymorphism) may inappropriately exclude therapy from some patients.
<b>Genelex CYP2C9 and VKORC</b>	CYP2C9*1, *2, *3 and VKORC1 -1639	Warfarin dosing[18]	Screening explains only approx 40% of dosing variation[84].
<b>HLA-B*1502</b>	HLA-B*1502	Carbamazepine associated Stevens-Johnson Syndrome or toxic epidermal necrolysis in Asian populations[85].	Limited to patients of Asian decent.
<b>HLA-A*3101</b>	HLA-A*3101	Carbamazepine associated hypersensitivity reactions in European populations[78].	NNT equals 39 European patients, 56 Japanese patients and 83 patients of un-determined decent.
<b>HER2 (INFORMR HER2 FISH test, PathVysion® HER2 FISH test, PharmaDX® HER2 FISH test, Spot-Light® HER2 CISH test)</b>	Number HER2 gene copies	Herceptin efficacy in breast[86] and gastric[86] cancer.	Equivocal results should be confirmed by a second screening method. 4 FDA approved genetic methods available.
<b>CYP2C19</b>	CYP2C19 metabolizer status	Poor metabolizers do not form active metabolite of clopidogrel[25].	Improved outcomes have been demonstrated in Chinese patients[30] only and no major society recommends genotyping prior to therapy to date.
<b>G6PD</b>	G6PD mutation by semi-quantitative or spectrophotometric methods[64]	High risk of hemolysis in patients receiving dapsone, methylene blue, nitrofurantoin, phenazopyridine, primaquine, rasburicase, and toluidine blue[87].	Initial semi-quantitative analysis should be confirmed by spectrophotometric method due to wide variability of enzyme function.

PPV: positive predictive value

NNT: number needed to treat

Table 2

'Omics Screens for Cancer Therapeutics.

Cancer Type	Test	Therapeutic Impact	'Omic Category
<b>Breast Cancer</b>	HER2 by FISH	Response to trastuzumab[9,10]	Genomics
	HER2 by IHC	Response to trastuzumab[9, 10]	Pathology/Proteomics
	ER/PR by RT-PCR	Response to hormonal therapies[88–90]	Transcriptomics
	DPD by PCR	Fluorouracil toxicity[91]	Genomics
	PIK3CA Mutation Analysis	Resistance to trastuzumab in HER2 positive tumors[92]	Genomics
<b>Colorectal Cancer</b>	KRAS mutation analysis	Response to panitumamab, cetuximab[13]	Genomics
	BRAF mutation analysis	Response to panitumamab, cetuximab[15]	Genomics
	EGFR amplication by FISH	Response to cetuximab[93]	Genomics
	Thymidylate synthase by IHC	Resistance to fluorouracil or related agents[94]	Pathology/Proteomics
	UGT1A1 Molecular Assay	Increased risk of severe irinotecan toxicity[95]	Genomics
	DPD by PCR	Fluorouracil toxicity[91, 96]	Genomics
	PIK3CA Mutation analysis	Resistance to cetuximab salvage therapy[97]	Genomics
<b>Non-Small Cell Lung Cancer</b>	EGFR Mutation analysis	Response to gefitinib, erlotinib[98]	Genomics
	KRAS Mutation	Resistance to gefitinib, erlotinib[14]	Genomics
	ALK by FISH	Sensitivity to crizotinib[99]	Genomics
	ERCC1 by IHC	Resistance to platinum-based chemotherapeutics[100]	Pathology/Proteomics
	EGFR Amplication by FISH	Resistance to gefitinib, erlotinib, cetuximab plus paclitaxel, and carboplatin[101]	Genomics
	EGFR by IHC	Response to cetuximab plus chemotherapy[102]	Pathology/Proteomics
	TS by RT-PCR	Resistance to pemetrexed[103]	Transcriptomics
	UGT1A1 Molecular Assay	Irinotecan toxicity[104]	Genomics
	ALK by FISH	Response to crizotinib in metastatic disease[105]	Genomics
<b>Gastric Cancer</b>	HER2 by FISH	Response to trastuzumab[11]	Genomics
	HER2 by IHC	Response to trastuzumab[106,107]	Pathology/Proteomics
	ERCC1 by IHC	Resistance to platinum-based chemotherapies[108]	Pathology/Proteomics
<b>Melanoma</b>	BRAF Mutation Analysis	Response to vemurafenib[16]	Genomics
<b>Brain Cancer</b>	MGMT methylation	Response to temozolomide[109]	Epigenomics
<b>Head and Neck Cancers</b>	DPD status	Fluorouracil toxicity and efficacy[110]	Metabolomics
<b>CLL</b>	17p by FISH	Resistance to fludarabine based regimens	Genomics
	P53 Mutation analysis	Resistance to fludarabine based regimens[111]	Genomics
<b>CML</b>	BCR-ABL	Recommended imatinib[112]	Genomics
	BCR-ABL KD Mutation V299L, T315A, F17L/V/I/C	Response to nilotinib rather than dasatinib[41]	Genomics

Cancer Type	Test	Therapeutic Impact	Omic Category
	BCR-ABL KD Mutation Y253H, E255K/V, F359V/C/I	Response to dasatinib rather than nilotinib[41]	Genomics
	BCR-ABL transcript mass by RQ-PCR	Response tyrosine kinase inhibitors after therapy ihas been initiated[113]	Transcriptomics
<b>Myelodysplastic Syndrome</b>	Deletion 5q	Response to lenalidomide[114]	Genomics
	Platelet derived growth factor receptor beta	Indication for imatinib[115,116]	Genomics
<b>Non-Hodgkin's Lymphoma</b>	MYC translocations	Resistance to retuximab plus cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) in diffuse B-cell lymphoma[117]	Genomics

HER2: Human epidermal growth receptor 2

FISH: Fluorescence in situ hybridization

IHC: Immunohistochemistry

ER/PR: Estrogen receptor/progesterone receptor

DPD: Dihydropyrimidine Dehydrogenase

PIK3CA: Phosphoinositide-3-kinase, catalytic alpha

EGFR: Epidermal growth factor receptor

TS: thymidylate synthase

ERCC1: Excision repair cross-complementing 1 protein

UGT1A1: Uridine diphosphate glucuronosyltransferase 1A1 gene

ALK: Anaplastic lymphoma receptor tyrosine kinase

MGMT: methylguanine-methyltransferase promoter