Impact of genomic data on building RWE for R&D

Rapid growth in the magnitude, complexity, penetration and adoption of RWD has enabled many critical insights, raised the efficiency of R&D, improved clinical effectiveness and accelerated the path to patient care. Genetic and biomarker data is increasingly being used to enhance traditional RWD evidence platforms to better understand and characterize disease pathways and to establish associations with phenotypic expression. Augmenting "translational medicine", this expanded role of genomic data brings potential to drive significant change across the R&D pipeline.

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Powering a more sophisticated drug development process

Human genetic data is fast becoming a significant component of the RWD landscape because of its increased availability and more sophisticated, broad-based applications. Growth in its scale, frequency and accessibility reflects rapid advances in sequencing and information technologies as well as the ability to quickly and cost-effectively analyze massive amounts of data enabled by government and private investment.

Genomic information, integrated with other types of RWD, is transforming the drug and clinical development lifecycle and pipeline. The convergence of this data with existing payer, provider, prescription, clinical trial and patient voice data enables sophisticated approaches to R&D that are more focused on the collective illustration of a patient's individual genotype and phenotype.

Growing role of genomics and RWD in R&D

In cancer and cardiovascular disease, clinicians and researchers can routinely access, use and understand disease-specific genetic profiles to inform patient care and explain clinical phenotypes and outcomes. This capability is analogous to simple lab test values and not typically linked with the broader aspects of RWD that can provide significant value to the R&D process. The ability to complement genomic data with additional RWD sources such as EMR, prescription, patient voice, ancestry, environmental and socioeconomic data will advance understanding of disease pathology, enable the prediction of medical outcomes and promote the realization of precision medicine (eg, government-sponsored programs such as President Obama's Precision Medicine Initiative and the UK's 100,000 Genomes Project).
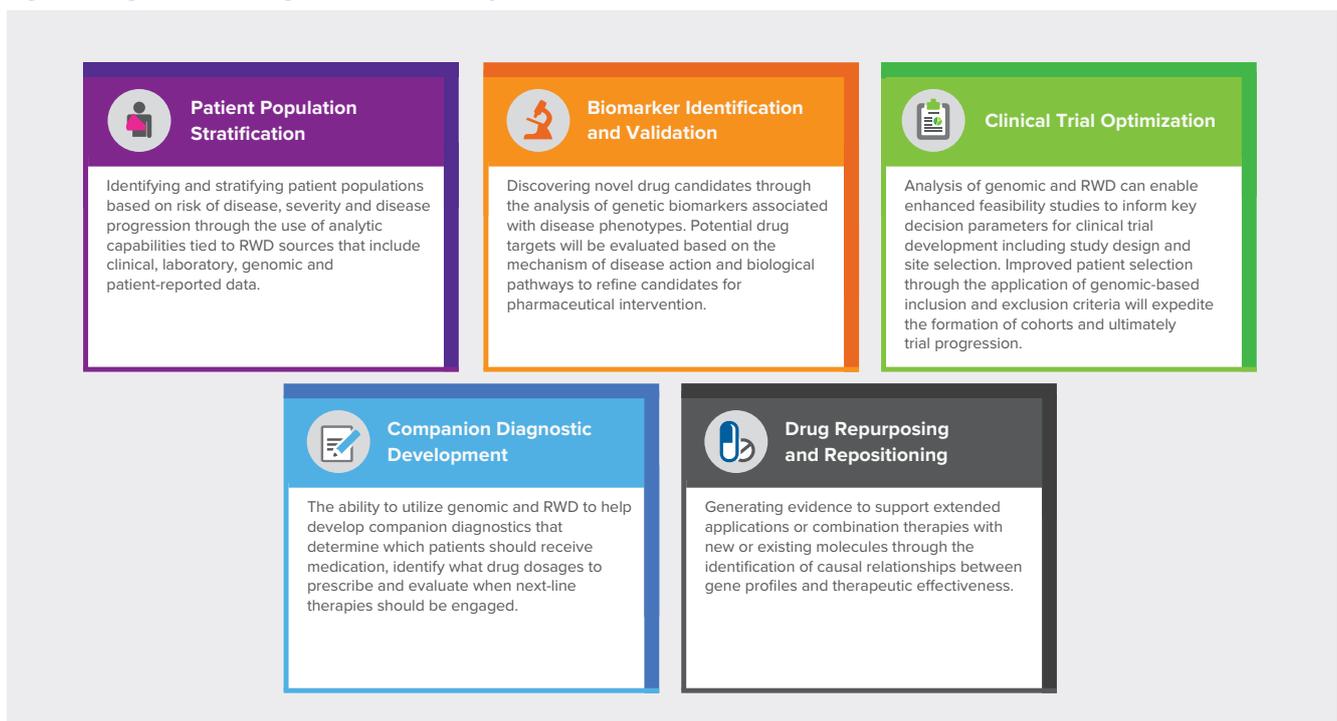
The impact of RWD integrated with genomic data is emerging throughout the drug development pipeline. Since the FDA started tracking pharmacogenomic information for all approved drugs in 2009, the number of FDA approved drugs with pharmacogenomics information in their labeling has grown to over 160 drug/biomarker pairs.[1] As the role of genetic information in drug development continues to expand, the number of drugs with reported pharmacogenomic effects is anticipated to increase. Of the 41 novel new drugs approved by the FDA in 2014, 9 (22%) are classified as a personalized medicine treatment that uses biological markers to guide prescribing practices.[2] These trends support an important and emerging role for genomic and RWD across the drug development process.

Key areas of influence

An RWD platform that is fully integrated with genomics and other "omics" translational data that is appropriately secured to protect privacy can play a pivotal role in the drug development R&D process, influencing the following five areas: patient population stratification; biomarker identification and validation; clinical trial optimization; companion diagnostic development; and drug repurposing and repositioning (Figure 1).

Figure 1: Integrated RWD and genomic data – five key areas of influence

Patient Population Stratification

Identifying and stratifying patient populations based on risk of disease, severity and disease progression through the use of analytic capabilities tied to RWD sources that include clinical, laboratory, genomic and patient-reported data.

Biomarker Identification and Validation

Discovering novel drug candidates through the analysis of genetic biomarkers associated with disease phenotypes. Potential drug targets will be evaluated based on the mechanism of disease action and biological pathways to refine candidates for pharmaceutical intervention.

Clinical Trial Optimization

Analysis of genomic and RWD can enable enhanced feasibility studies to inform key decision parameters for clinical trial development including study design and site selection. Improved patient selection through the application of genomic-based inclusion and exclusion criteria will expedite the formation of cohorts and ultimately trial progression.

Companion Diagnostic Development

The ability to utilize genomic and RWD to help develop companion diagnostics that determine which patients should receive medication, identify what drug dosages to prescribe and evaluate when next-line therapies should be engaged.

Drug Repurposing and Repositioning

Generating evidence to support extended applications or combination therapies with new or existing molecules through the identification of causal relationships between gene profiles and therapeutic effectiveness.

1. **Patient population stratification**

The integration of genomic data with other RWD sources can enable further stratification of populations leveraging multiple clinical indicators and modeling algorithms. The combination of clinical diagnoses, lab test data and genomic information can be used to identify and stratify patient sub-populations to support biomarker identification, predictive analytics or prospective study development. These Enriched RWD studies are emerging from RWE concepts where retrospective studies can influence or guide the planning and execution of prospective studies throughout the drug R&D process. The value of combining retrospective and prospective data is quickly emerging in the industry and is exemplified by the Enriched RWD approach discussed in the article on page 11 of this issue. This approach will enable the generation of immense, rich data sources to support drug development, clinical trial design and the establishment of characterized populations for clinical trial inclusion.

The inclusion of patient- and population-level genomic data extends these capabilities even further, providing additional data on the patient's genetic risk for developing a disease or effectiveness of response to treatment. This approach will also identify and interpret the retrospective study data and can be used to inform the design, sample size and study population for the prospective analyses. The integration of genomic information across all real-world datasets affords valuable intelligence that can elucidate retrospective patient data or assist in the development of prospective cohorts. This knowledge can be applied in multiple platforms to provide value analysis and support throughout the drug development lifecycle.

2. **Biomarker identification and validation**

As the age of blockbuster drugs wanes and the era of personalized medicine emerges, genetic and epigenetic biomarkers are being identified and utilized more frequently to provide greater specificity for how individual genetic variation impacts drug response and disease progression. This data is traditionally heralded as "translational" or bench-to-bedside in nature; however, combining it with other RWD sources can greatly expand its value to all stakeholders such as payers, providers, researchers, advocacy groups and, most importantly, the patient.

There have already been assessments made on the value of genetic evidence to support drug development mechanisms. A recent study found that the number of drugs developed with direct genetic support significantly increased along the development pipeline, growing from approximately 2% at the preclinical stage to over 8% for approved drugs.[3] Furthermore, the authors estimated that through the application of genomic information, companies could effectively double the success rate for drug development.

Using this model, researchers can couple genomic information with RWD to rapidly discover new biomarkers for drug targeting. They perform such analysis by querying a large patient dataset to identify a disease cohort of interest and match it to a healthy control population. By comparing the selected disease cohort with the matched control, they can identify genomic variants that are significantly over- or under-represented in the disease population. This information can be linked to other RWD, internal client data and published research studies to further refine and determine the molecular mechanisms of disease. They will then be able to identify biologically relevant targets for pharmacological intervention.

This methodology has several advantages that will accelerate the drug development process by enabling researchers to

- Identify and query cohorts on demand without the need for costly patient recruitment, consent and sample sequencing

- Further augment or refine the disease cohorts in real time, analyzing co-morbidities and other demographic information without the need for additional recruitment

- Molecularly tailor therapies based on the actual mechanism of the disease and apply this knowledge throughout the drug development pipeline

3. **Clinical trial optimization**

The utilization of RWD to optimize trials has traditionally served to evaluate the past history and performance of existing clinical trial sites and physicians or to evaluate EMR data across a broad spectrum of providers to identify qualifying patients. As the industry focuses on characterizing the molecular models of disease, the patient-level approach for clinical trial inclusions will emerge as a more effective method for hard-to-recruit trial populations.

The recently initiated NCI-Molecular Analysis for Therapy Choice (NCI-MATCH) program is one example of how genomic information can guide clinical trial recruitment and participation. The study explores the use of new molecularly defined indications of previously approved cancer drugs. Over 4,000 genetic variants in 143 genes will be analyzed and used to inform enrollment of specific arms of the clinical trial to investigate the efficacy of more than 20 cancer drugs.[4]

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This will enable analysis of drug efficacy in specifically defined cohorts to improve clinical trial results.

Genomic information and RWD can provide value at several points during the design, implementation and analysis of clinical trials

- **Support feasibility studies** by affording analysis of patient populations, study sites and clinical trial design to maximize the efficiency of the clinical trial prior to implementation. Using this information, clinical trial study parameters can be adjusted to maximize the trial's speed and effectiveness.

- **Help establish patient cohorts and inclusion/exclusion criteria** to further support clinical trial optimization. For drugs that are designed to target a specific molecular pathway or gene variant, biomarker data can provide valuable information to guide the selection of patients for the case and control cohorts.

- Provide additional insight to **further classify the clinical trial population** based on molecular signatures to ensure more targeted inclusion/exclusion criteria. Clinical trials designed in this targeted manner will require a smaller study population, thereby speeding up the process and reducing costs.

- **Inform adaptive clinical trials** by enabling study cohorts to be further characterized and refined throughout the clinical trial to provide additional insights on drug safety and efficacy. This information will determine pharmacogenomic effects to support modifications to the drug dosage, patient inclusion/exclusion criteria or clinical trial sample size. The integration of these data sources in adaptive clinical trials will identify drugs that have therapeutic effect within a targeted sub-population to facilitate the expedient approval of new molecular compounds.

4. **Companion diagnostic development**
   A companion diagnostic is any test that provides additional information to guide the safe and effective use of a treatment. These tests can be used to identify patient populations that will beneficially respond to a particular drug or to identify sub-populations of patients that have an increased risk for an adverse drug event.

   When a drug has been developed in conjunction with data on the disease pathology and mechanism of drug action, the target patient population can be defined on a molecular level. A companion diagnostic can then be concurrently designed to test for biomarkers relevant to this cohort and used to inform study design for clinical trial development. Under this model, the clinical trial serves not only to validate the safety and efficacy of the drug but also to confirm and clinically validate the companion diagnostic. As such, clinical trial participants are tested using the companion diagnostic and only the patients with the appropriate biomarkers are enrolled in the study.

   Companion diagnostics can also be developed through retrospective analysis of clinical trial data, for example, in cases where the investigational compound has caused significant adverse events or only displayed efficacy within a trial's sub-population. Here, genomic data from clinical trial participants is analyzed to provide insight on pharmacogenomic effects linked to the drug response. Once the genetic variant(s) have been identified, companion diagnostics can be developed and validated to support approval of the new drug. This will ensure that future adverse events are prevented and/or the drug is made available for patients who respond positively to the medication.

5. **Drug repurposing and repositioning**
   Many drugs are designed to act within a certain molecular pathway to treat or prevent disease. By integrating information on how the drug acts on a disease target, a disease's mechanism of action and the structural similarity of drug compounds, new treatment paradigms will emerge. The additional insight afforded on novel therapeutic applications can be applied to investigational compounds, approved drugs on the market or innovative combinations of both. In recent years, studies have established molecularly defined groups of diseases called diseasomes to identify new applications for FDA approved medications. This approach is already transforming oncology as cancer types which were once identified based on the organ(s) impacted can now be defined based on genetic mutations and molecular pathways.

   Typically, product positioning can be determined using one of two computational methods

   1. Focus on the drug itself to identify new targets or binding partners for the chemical compound

   2. Focus on the molecular pathophysiology of the disease to identify shared pathways[5]

   These approaches not only provide a more comprehensive understanding of the disease and treatment options but also identify new applications for previously approved drugs with known safety profiles.

Using these strategies, companies will be able to bring newly positioned drugs to market at a much faster rate as the regulatory approval process for repositioned drugs is often much shorter than for a new molecular compound.

An additional application is supporting the development of combinatorial therapies in which multiple drugs are targeted to act on discrete components of a cellular pathway. By targeting multiple components of a defined disease pathway, novel therapies can be developed to more effectively treat or prevent disease.

Advancing the vision of precision medicine

The application of genomic data within RWD is poised to drive significant changes across the drug R&D pipeline. With the rapid development of sequencing and analysis technologies, the use of genomic data will soon become routine in the development of many types of drugs.

Even beyond the uses discussed here, the value of this data can contribute to a significantly broader set of capabilities including heredity studies, adaptive licensing, safety & efficacy, pragmatic clinical trials and unmet needs analysis. As genomics and the broader array of traditionally "translational" evidence are integrated into RWD, a tremendous opportunity emerges to advance the vision of precision medicine.

IMS Health can integrate genomic information into incredibly sophisticated networks of real-world datasets to provide a comprehensive resource to support the development of retrospective, prospective and Enriched RWD studies. The addition of predictive analytic tools can be used to further develop an understanding of the patient's journey through population-level assessments of phenotypes and genotypes. The patient's genetic profile, the mechanism of disease action and the patient's manifestation of health and disease paint a comprehensive picture of their journey as it relates to nearly any health risk or condition. Through the integration of this information and advanced analytic tools, IMS Health can provide a comprehensive platform to support the drug development lifecycle as the world of precision medicine progresses.

1   http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm

2   http://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/2014-fda-approvals-personalized-medicine2.pdf

3   Nelson MR, Tipney H, Painter JL, Shen J, Nicoletti P, Shen Y, Floratos A, Sham PC, Li MJ, Wang J, Cardon LR, Whittaker JC, Sanseau P. The support of human genetic evidence for approved drug indications. Nat Genet, 2015, Aug; 47(8): 856-60

4   http://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/nci-match

5   Dudley JT, Deshpande T, Butte AJ. Exploiting drug-disease relationships for computational drug repositioning. Brief Bioinform, 2011, Jul; 12(4): 303-11

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