

Pharmacogenomics checklist

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Are you about to initiate a pharmacogenomics study? For successful results be sure to consider all the options before you start...

The recently issued guidance from the FDA on submission of pharmacogenomic data has increased interest within the pharmaceutical industry towards the application of pharmacogenomics in drug development. While their clinical colleagues are exploring alternative development strategies for drug approval using pharmacogenomics, many drug discovery researchers are re-examining how genotyping studies can be best integrated into therapeutic research programs.

Some pharmaceutical companies are designing pharmacogenomic studies of drug candidates (and drugs on the market) in order to gain information for clinical development, as well as for discovery programs directed at identifying the biological activity of new chemical entities. Whatever the purpose of a pharmacogenomic or genotyping study, there are a number of key decisions to be made before the project is initiated, as discussed below.

Before you start...

Type of study

The underlying reason for embarking on genotyping of patient samples is to determine the genetic basis of the trait, or phenotype, being examined. Ideally, one should select a study where there is evidence for a genetic basis to the phenotype. Pharmacogenomics examines the genetic basis of drug response while discovery genetics investigates the genetic basis of a disease. Both types of project make use of genotyping technology.

Drug response

In a pharmacogenomics study, the DNA of patients who respond favorably to a drug is compared to the DNA of patients who do not respond favorably. The phenotype being examined can be either efficacy or a side effect of the drug.

Clinical trial/market status

Due to the number of patient samples required to achieve sufficient statistical power in a pharmacogenomic study, the genetic basis of a drug's efficacy can generally be examined starting in early phase III, while the genetic basis of a drug's side effect can generally be examined starting in late phase III, depending on the incidence of the side effect and the number of patients treated for whom DNA samples are available.

Disease state

Phenotypes should be as precisely defined as possible; DNA samples from patients with the phenotype being examined are compared to DNA samples from matched people who do not exhibit the phenotype.

Case/control populations

Genotyping projects are conducted as classical case/control genetic association studies. The cases exhibit the phenotype. The controls do not exhibit the phenotype and are matched to the cases. Sometimes other phenotypes can be used as controls.

Study design

In genotyping projects, one can either examine the whole genome, certain parts of the genome, or candidate genes. While most genotyping studies to date have focused on candidate genes, the technology now exists to comprehensively examine the entire genome of patients when seeking to identify genetic associations. The clear advantage of the whole genome approach is that there is no information needed a priori about where the genetic association is likely to be. This is especially important in pharmacogenomic studies of drug response, because unlike discovery genetics studies of patients with a particular disease (where many publications on the genetics of that disease may exist), the researcher is unlikely to find scientific literature describing genetic variants associated with response to the drug. Of course, since we don't know the identity of most disease-predisposing genes and since researchers are often unable to replicate genetic associations in published candidate gene studies, conducting a whole genome association study is also an advantage even when candidate genes are available.

Whole genome association

Today, it is scientifically possible and commercially feasible to genotype (interrogate) over 1.5 million genetic variants (single nucleotide polymorphisms or SNPs) in each patient's genome within a whole genome association study. This number of variants results in a map of the human genome with a genetic marker approximately every 2000 bases. As a result, unlike earlier efforts at whole genome scanning that, at best, resulted in associated

genetic markers tens of thousands of bases away from the causative genetic variant, it is possible today to find a correlation with genetic markers within the causative gene or regulatory element, or very close to it. This facilitates the development of a diagnostic based on a genetic fingerprint.

Partial genome association

While there are many ways to segment the genome so that only certain parts of the genome are interrogated in an association study, some of the more common approaches are interrogating only the SNPs identified in the exons of all known genes, or only the SNPs identified in all known genes that change an amino acid.

Candidate gene association

In a candidate gene association study, the genes of interest are specified beforehand. Typically, in each candidate gene association study up to 100 genes are identified in contiguous segments of 100 kb. Within this 10 Mb of genomic sequence, approximately 7500 SNPs can be interrogated to provide a map density comparable to that available for whole genome association studies.

Replications

Once genetic markers (genetic loci) have been associated with a phenotype in a population, the results must be replicated in a different set of samples.

Assays

With certain genotyping technologies, one factor that can limit the breadth of the study is the availability of an assay for each SNP and/or the upfront cost to purchase assays for the SNPs to be interrogated.

Samples

Samples in genotyping studies should be well characterized, ideally with complete medical histories available. In order to assure statistical significance of results and to achieve the statistical power to reveal genes with as low as a 2-fold relative risk, researchers should aim to collect samples from 200 to 500 cases and 200 to 500 controls. It is possible to have a study design encompassing more controls than cases. Since controls are generally easier to collect, this can be a way of increasing the statistical power of studies where the full complement of cases is not available.

Sufficient DNA

It is important to plan for the collection of sufficient DNA per sample to conduct genotyping. The amount of DNA required varies depending on the genotyping technology used and the study design. Amplification technologies may significantly reduce the amount of DNA required. Since genotyping methodologies are destructive to the sample being tested, DNA should be retained for replication and other purposes.

Informed consent

Informed consent obtained from patients must permit genetic analysis of patient samples. When samples are sent to third parties, they should be de-identified.

Handling of samples

DNA for genetic analysis is generally obtained from blood of patients. Whole blood or DNA can be shipped to third parties for analysis. Blood samples can be shipped frozen without degradation to the DNA.

Research plan

Depending on the technology utilized, genotyping studies can be conducted in-house or at laboratories of companies conducting such studies. It is also possible to develop a research plan that has some genotyping conducted in-house and other genotyping conducted at the laboratory of a collaborator. This may be desirable, especially when the collaborator is a company that has a proprietary genotyping technology.

Timeline

Genotyping related to whole genome association studies can be completed in a remarkably fast time. The laboratory work related to genotyping can usually be completed in days or weeks, rather than the months that it previously took. Since over 100 million genotypes may be performed in a typical whole genome association study, the throughput today dwarfs that possible only a couple of years ago.

Looking to the future

As pharmacogenomic technologies progress from the "early developmental stage," as described by the FDA in its recent guidance document, to fully accepted methodologies for use in clinical development and elsewhere, many in the industry expect that pharmacogenomic submissions to the FDA will become the norm, or even a requirement of NDA filings. In parallel with this, the genotyping technologies underlying these pharmacogenomic submissions will find increased use in both clinical and preclinical aspects of drug discovery and development.

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