Pharmacogenomics

Faculty Presenter

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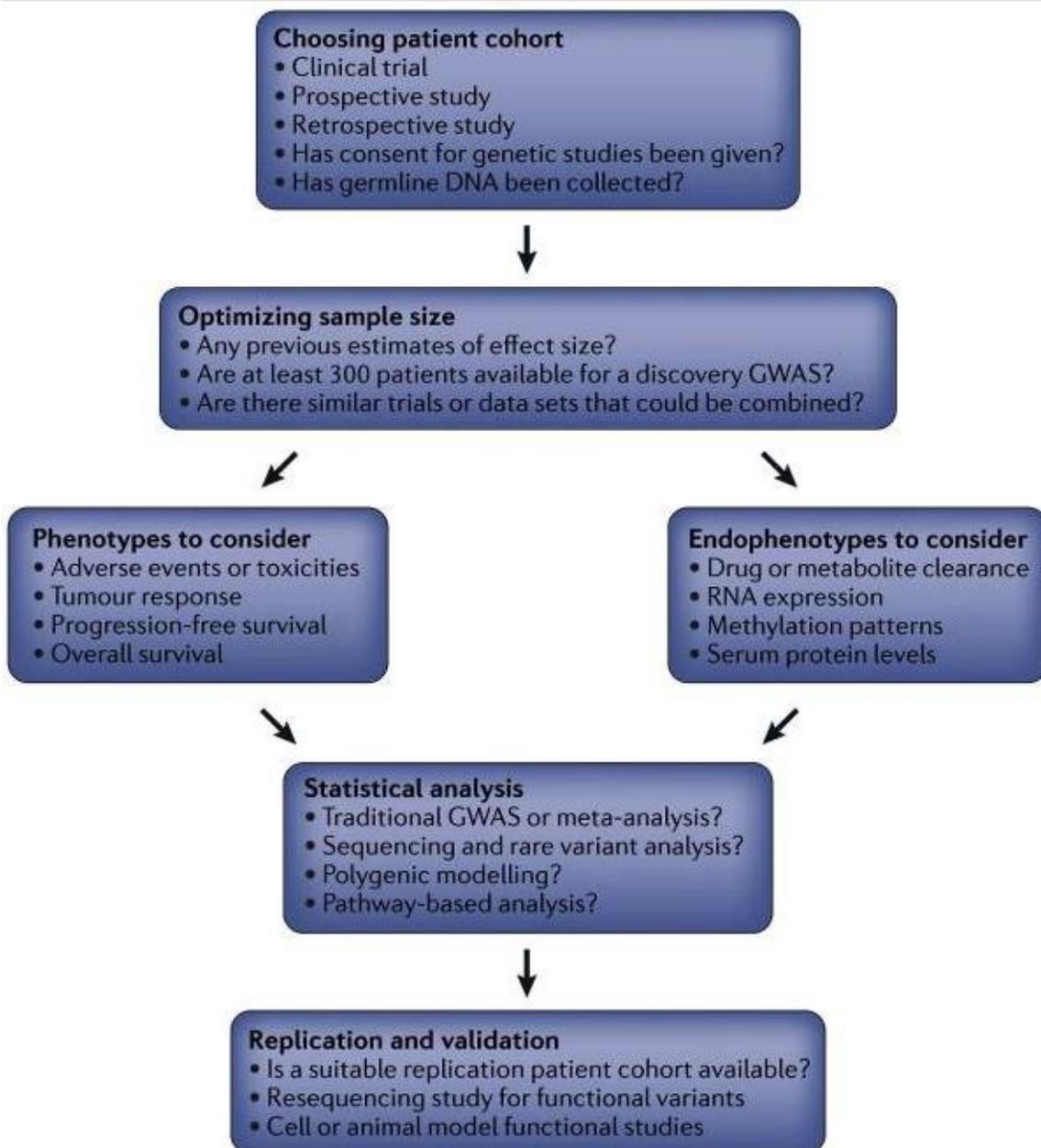
Pharmacogenomics is the study of the effect of genetic variation on drug response or toxicity. This study comprised a critical part of the Precision Medicine Initiative launched by President Barack Obama in 2015, which was designed to "...give us all access to the personalized information we need to keep ourselves and our families healthier."
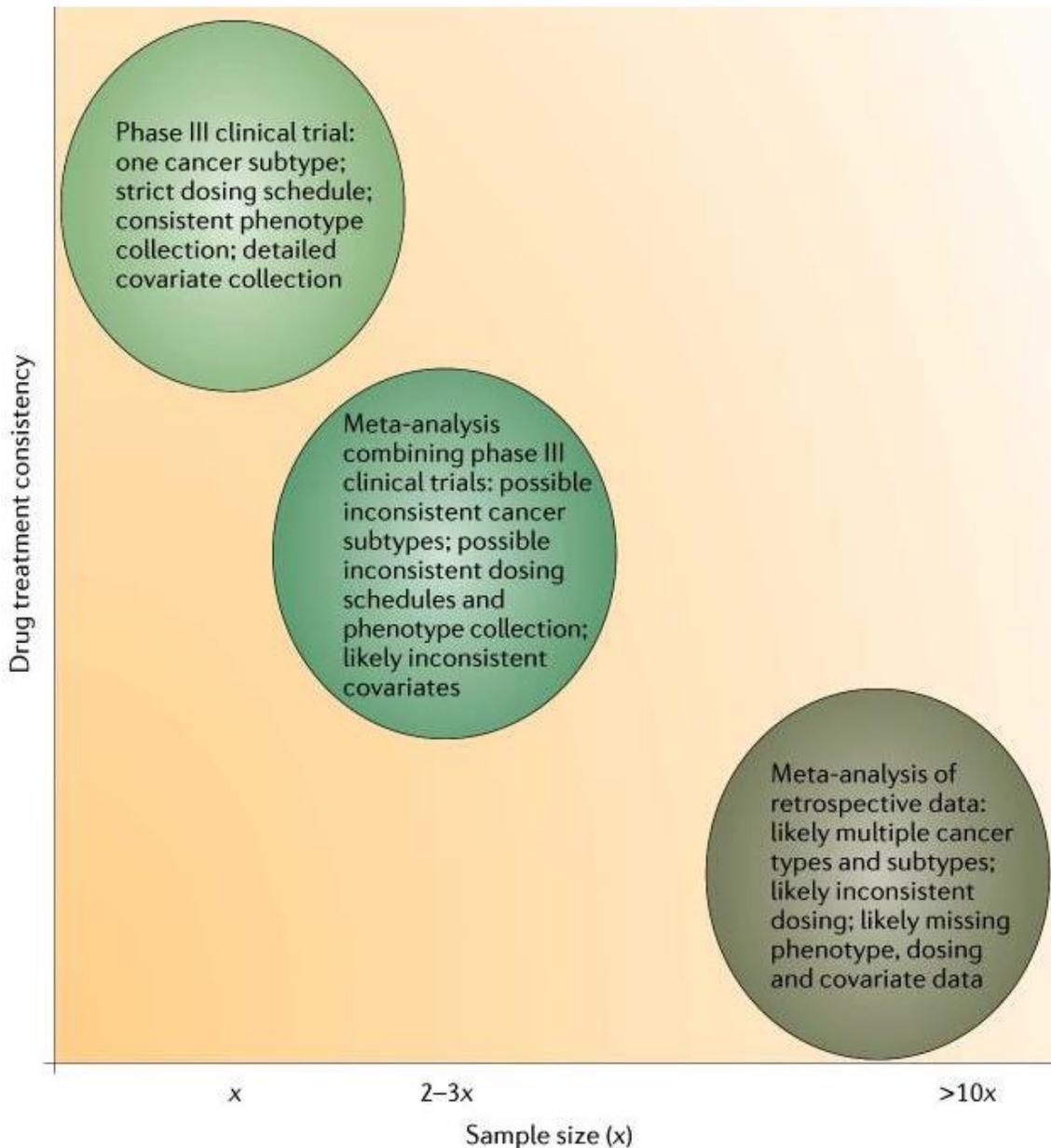
In oncology, research into pharmacogenomics identifying molecular diagnostic tools that can be used for better drug selection and dosing of anticancer agents is an important consideration given their often narrow therapeutic index and associated toxicities. Both inherited (germline) and acquired (somatic) variability sources can significantly alter both the efficacy and safety of anticancer therapies.[1] There is a strong need for better prescribing guidance in general in this country. Adverse drug reactions are the fifth leading cause of in-hospital death in the United States. In addition, efficacy rates for even the most common drugs treating the most prevalent diseases are approximated at only about 50%, and the healthcare system wastes millions of dollars on poor prescription drug choices.[2-4] For example, at the end of the first decade of this millennium, simvastatin was the second most prescribed drug in the United States, with 83 million prescriptions written annually. However, the drug was only one of several choices for treating hypercholesterolemia, including other statins and non-statin alternatives. In addition, simvastatin use was limited by its tendency to create severe myopathy in patients using the drug.[5] However, pharmacogenomic research has identified genetic variants that may identify patients at risk for myopathy while taking statins, such as the *SLCO1B1* variant on chromosome 12 than has been found to be strongly associated with statin-induced myopathy.[6]

Oncologists are a prime group for using pharmacogenomics in clinical practice. Data have shown that they are already more experienced in ordering pharmacogenetic testing, feel sufficiently informed about the use of this type of testing in practice, and are able to interpret results and discuss these results with their patients.[7] Patients may actually act as drivers for the use of pharmacogenetic testing. Their likelihood to be agreeable to testing is high in many situations, including predicting mild or serious side effects of therapy (73%), predicting initial dosing (91%), and assisting with drug selection (92%).[8] That said, the actual readiness of the physician population in the United States to use pharmacogenetic testing/precision medicine is still questionable. A study by Stanek, et al, in 2012 of >10,000 American physicians found that 98% believed genetic profiles could influence drug therapy, and only 13% of those surveyed had ordered a pharmacogenetic test in the last 6 months. Still, 26% believed they would order such testing in the next 6 months, but only 10% claimed to be adequately informed about this type of testing.[9]

In publications surrounding cancer drugs, some data demonstrated that 56% of publications identified were pharmacogenomic publications, with an 82% rate of multiple positive publications. The most common outcomes that are studied for pharmacogenomic association include progression-free survival (PFS), overall survival (OS), response rate, hematologic toxicity, neurotoxicity, and hepatotoxicity. Several well-known oncology drug examples exist. Looking at the drug mercaptopurine, for example, activity of the enzyme thiopurine S-methyltransferase (TPMT) is variable, based upon polymorphism within the gene. Genotyping can delineate specific alleles associated with distinctive levels of enzyme activity. This can help identify patients who have inherited inactive TMTP alleles who might experience severe myelosuppression with purine therapy, including patients who are either homozygous or heterozygous deficient, allowing individualized drug dosing.[10] Similarly, genetic testing may be used to identify other at-risk individuals, such as those with the *UGT1A1* genotype that has been strongly associated with severe neutropenia in patients with cancer treated with irinotecan, and that could be used to identify cancer patients predisposed to this severe toxicity and to guide irinotecan dosing.[11,12]

Multiple pharmacogenetic studies have been performed surrounding therapy in patients with cancer, and several steps are required in study design surrounding discovery of pharmacogenetic markers[13]:

Choosing patient cohort
- Clinical trial
- Prospective study
- Retrospective study
- Has consent for genetic studies been given?
- Has germline DNA been collected?

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Optimizing sample size
- Any previous estimates of effect size?
- Are at least 300 patients available for a discovery GWAS?
- Are there similar trials or data sets that could be combined?

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Phenotypes to consider
- Adverse events or toxicities
- Tumour response
- Progression-free survival
- Overall survival

Endophenotypes to consider
- Drug or metabolite clearance
- RNA expression
- Methylation patterns
- Serum protein levels

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Statistical analysis
- Traditional GWAS or meta-analysis?
- Sequencing and rare variant analysis?
- Polygenic modelling?
- Pathway-based analysis?

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Replication and validation
- Is a suitable replication patient cohort available?
- Resequencing study for functional variants
- Cell or animal model functional studies

Phase III clinical trial: one cancer subtype; strict dosing schedule; consistent phenotype collection; detailed covariate collection

Meta-analysis combining phase III clinical trials: possible inconsistent cancer subtypes; possible inconsistent dosing schedules and phenotype collection; likely inconsistent covariates

Meta-analysis of retrospective data: likely multiple cancer types and subtypes; likely inconsistent dosing; likely missing phenotype, dosing and covariate data

Drug treatment consistency

Sample size (x)

x   2–3x   >10x

As another example, dihydropyrimidine dehydrogenase (DPD) deficiency has been linked to severe toxicity in response to cancer therapy with 5-fluorouracil (5-FU) and has been demonstrated repeatedly, with up to 30% of patients treated experiencing severe 5-FU-related toxicity.[14,15] Genetic research and testing of these patients has led to the FDA label for this agent listing DPD deficiency as a consideration, stating that topical and oral 5-FU "should not be used in patients with known DPD deficiency," along with published guidelines providing precautions for use of intravenous 5-FU and recommending the use of dose-adjustments (with possible subsequent up-titration) in patients with known partial DPD deficiency, and avoidance of 5FU and related drugs in patients with homozygous deficiency.[16,18] Research has identified >40 different mutations and polymorphisms in *DPYD*, the gene that produces DPD. While most of these variants have no functional consequences on enzymatic activity, some have received particular attention for their functional consequences. Particular interest was shown in the IVS14 +1 G>A variant (*DPYD*2A*) that has been found in 40% to 50% of patients with partial or complete DPD deficiency.[17] Current research now suggests that upfront genotyping ("screening") may not only be clinically advantageous to identify patients with *DPYD* polymorphisms but also may provide overall cost savings, with lower total care costs found when comprehensive screening is implemented before starting any 5FU-based therapy.[19]

Despite all these advances, several barriers to clinical pharmacogenomic implementation exist. These include lack of routine availability of pharmacogenetic tests, delays in obtaining results, lack of physician knowledge about these tests, and

concerns about interpretation of results and translation into actual clinical practice. In addition, both the clinical relevance of overall current pharmacogenomic evidence and the costs related to screening remain in debate.

To attempt to remedy and study some of these implementation challenges, The 1200 Patients Project was initiated at the University of Chicago Center for Personalized Medicine, and it focused on four main elements[20-24]:

- Technical: creating customized pharmacogenomic test panels to accurately measure genotypes
- Translation/Education: creating clinical summaries of the pharmacogenomic literature for use in interpreting tested genotypes
- Knowledge Transfer: electronic disseminations and instantaneous availability of results for access at any clinical moment/need
- Implementation Science: measuring the results of deploying the pharmacogenomic intervention for best prescribing

Using this model, patients undergo preemptive pharmacogenetic testing, and a composite summary of their pharmacogenomics risk for all known actionable drugs (oncology and otherwise) is made available to their treating physicians. Potential alternative drugs that may be safer and more effective based on the patient's particular genotype(s) are also shown. For example, in the case of mercaptopurine use, a patient might be identified as having a *TPMT* genotype that confers deficient activity enzyme status for catabolism of this agent, resulting in possible serious or even fatal myelosuppression if mercaptopurine is administered. This could allow the recommendation of an alternative immunosuppressant for nonmalignant disease or a dose reduction/administration reduction in the case of malignant disease.[20-24]

The project currently has reportable information for 51 medications, more than 100 germline variants, and >40 genes. Oncology drugs with germline pharmacogenomics include capecitabine/fluorouracil, doxorubicin, irinotecan, mercaptopurine, ondansetron, and tamoxifen. Current enrollment is 1218 patients (85% of the 1425 approached for inclusion). Of these, 40% were enrolled from primary care, with 14% from oncology. At 89% of patient visits, pharmacogenomic information was available for at least 1 drug the patient was taking.[20-24]

It is to be hoped that future directions will include outcomes measurements showing a decrease in adverse and non-response events with use of pharmacogenomic information at the point-of-care, identification of haplotypes and as-yet-undiscovered rare variants to better understand individual risk, integration of tumor and germline information, and facile assimilation into the electronic medical record (EMR). However, one overriding obstacle must be addressed, namely: who will pay for this information? Future efforts in the movement to bring truly precision/personalized medicine to all patients with cancer will have to overcome this and other identified barriers to achieve universal implementation.

Summary:

Pharmacogenomics/pharmacogenetic testing is a prime focus area for oncologists today. Data from studies looking at the effects of genetic polymorphisms and particular patient phenotypes affecting use of drugs such as mercaptopurine, irinotecan, and 5-FU has led to identification of genetic variants related to drug toxicities and potentially serious adverse events, allowing dose adjustments or therapy switches to protect these patients. While several barriers still impede more consistent adoption of pharmacogenomics in clinical practice, efforts including The 1200 Patients Project among others are identifying new methods to accurately genotype patients with cancer and allow truly personalized medicine with the goal of enhancing treatment effectiveness, safety and patient outcomes.[20-26]

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