The mantra of many clinical trialists has been to do randomized clinical trials with broad eligibility and avoid subset analysis. Developments in cancer research, however, have raised some questions about this approach in the genomic era of molecularly targeted therapeutics.

A large body of evidence indicates that cancers of most primary sites are heterogeneous with regard to molecular pathogenesis, genomic signatures and phenotypic properties. Consequently, it is not necessarily reasonable to expect such tumors to have equal sensitivities to a drug that inhibits a particular protein target. The protein target may be driving tumor growth in only a subset of the tumors.

As an example, two large randomized clinical trials were recently reported comparing standard therapy to standard therapy plus a new drug, Iressa, for patients with lung cancer [1,2]. Both trials were convincingly negative. Nevertheless, the US Food and Drug Administration approved the drug based on the recommendation of an advisory committee. The approval resulted from evidence of durable partial tumor response in about 10% of patients with advanced lung cancer in an uncontrolled phase II study. Subsequent publications indicated that patients who responded in the phase II trial were those whose tumors had a mutation in the kinase domain of their EGFR gene, rendering those tumors highly sensitive to treatment with an epidermal growth factor receptor inhibitor such as Iressa [3,4]. This result, indicating that Iressa was highly effective for a small subset of cases and that large randomized clinical trials of unselected patients failed to identify the value of the drug, has provided a stimulus to think about clinical trial methodology for the evaluation of molecularly targeted drugs in oncology.

Clinical trials in which eligibility is restricted to those patients whose tumors are sensitive to the drug can be substantially more efficient than traditional clinical trials with broad eligibility. Some of the dramatic improvements in the possible efficiency have been indicated by Simon and Maitournam [5]. The improvement in efficiency results because the treatment effect is substantially larger in the focused clinical trial if there is a good assay available for selecting patients likely to respond to the new treatment. Such focused treatment can provide a more favorable benefit to complication ratio and result in a greater proportion of the treated patients benefiting from the treatment. This can also have important economic benefits for society. Currently, for some indications such as stage I estrogen receptor positive breast cancer, fewer than 10% of the patients treated with cytotoxic chemotherapy actually derive benefit from the drugs. The proportion may be even lower for prevention settings of cancer and other diseases.

It is important, therefore, to develop predictors of whether an individual is likely to benefit from a given drug. For some cancer treatments, predictors can be based on assays for the expression of the drug target. This is the case for tamoxifen and herceptin. In these cases, focused clinical trials with patients selected based on assay results greatly enhanced the efficiency of clinical development. For Iressa, expression of the epidermal growth factor receptor did not correlate with response during phase II development. In such cases, it is important to use the phase II development period to develop response predictors using other data. This may involve performing RNA expression profiling of tumors for patients in phase II trials or sequencing candidate genes looking for mutations that correlate with response.

RNA transcript expression profiling is a powerful approach for developing classifiers of tumor sensitivity to a particular drug [6–9]. There is...
a misconception among some clinical trialists that
the multiple comparison issues involved with gene
expression profiles preclude their effective use for
tailing therapy. The misunderstanding arises
partly from the failure to distinguish between
prediction and inference and partly from a concern
that gene expression data will be used as a basis for
data dredging in phase III clinical trials. In fact,
useful predictors can often be developed with quite
limited numbers of cases [10,11] and used as
completely specified classifiers in the design of
confirmatory phase III trials.

Most statistical methods were developed for
inference. The development of a multigene expres-
sion profile based predictor of outcome with an
experimental treatment based on phase II data is
a prediction problem. The objective should be
accurate prediction. The objective is not to ensure
that all the genes included in the predictor function
are necessary. In general, many genes are correlated
and the genes selected for inclusion in the model
may not be stable under replication or resampling
even if the predictions are excellent. The objectives
of developing such a predictor is different from the
objective of identifying what genes are correlated
with outcome. Although the development of out-
come predictors generally involves a “feature
selection” component, the multiple comparison
issues involving controlling the number of false
positive features included in the model is not of
direct concern. We do not really care about the false
discovery rate of genes, what we care about is
predictive accuracy.

Ideally, pharmacogenomic predictors are deve-
loped using phase II data so that they can be
utilized to increase the efficiency of phase III trials.
At the time the phase III trial is designed, a fully
specified predictor should be available. This pre-
dictor can be used to select patients for the phase III
trial [5], or as the basis of a single completely
predefined subset analysis in a phase III trial not
limited by preselection of patients. In either case,
the phase III trial is free from the problems of
data dredging.

Randomized clinical trials have been one of
the most important developments in modern
medicine and they will continue to be important.
Whole genome technologies make it more feasible
to develop disease classifiers which can make
randomized clinical trials much more efficient,
and treatments more effective. Such classifiers are
direly needed in fields such as cancer, where the
proportion of patients who actually benefit from
most treatments is quite low, and the economic
costs of treating the many for the benefit of the
few are enormous. The change from our current
approach to therapeutics development to a more
personalized approach is not likely to occur rapidly,
however. Technologically, the use of RNA transcript
profiling data is limited by the availability of tumor
tissue with preserved RNA. There are also many
other obstacles that must be overcome. The devel-
opment of traditional single protein biomarkers
has been ineffective in oncology [12–15]. There is a
lack of understanding among academic, industry,
and government scientists of effective paths and
appropriate requirements for development and
validation of therapeutically relevant biomarkers.
The development of profile biomarkers based on
high dimensional assays offer additional challenges
[16,17]. There are also important disincentives that
must be overcome on the part of drug sponsors and
clinicians. Pharmaceutical companies naturally
prefer products with broad labeling indications.
Development strategies, such as use of the
predefined subset approach described above, must
be identified that enable companies to invest in the
development of pharmacogenomic signatures with-
out the risk of losing broad labeling indications
where supported by the results of phase III trials.

The randomized clinical trial remains a generally
indispensable tool for the final evaluation of inter-
ventions. But genomic technology provides the
opportunity to tailor treatments to those patients
most likely to benefit. This is important for
individual patients and essential for our societal
health care budget. Biostatisticians and clinical
trialists have made enormous contributions to
medicine and should be proactive in addressing
the important challenges involved in effectively
combining these two areas.

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