Note: An f following a page number refers to a figure on that page; a t following a page number refers to a table following that page.

#### adaptive

eligibility, 55-57 randomization, 31 adaptive signature design, 72-73, 74 cross-validated, 75-79 fall-back test, 47-48 adaptive threshold design, 59-63 probabilistic indication classifier and, 60 - 62sample size planning, 62-63 aggregated Classification Trees, 117 algorithms class prediction, 112-118 genetic, 114 pre-specified algorithmic analysis plan, 72 analytical validity, 11, 88 baseline cumulative hazard, 122-123 baseline hazard function, 30, 120 Battle I trial in advanced non-small cell lung cancer, 30-33 results of, 31t, 31-32 two-stage design, 32-33 Bayesian methods, 101-103 adaptive designs for randomized phase II trials, 30-33

computing posterior probabilities, 102-103 estimating sensitivity and specificity, 124 frequentist methods versus, 101-102 loss function, 102-103 non-informative prior distributions, 103 posterior distributions, 102 prior distributions, 102, 103 probabilistic indication classifier, 61 Type I error, 103 usefulness in phase 3 trials, 103 binary disease classification, 124-125 biomarkers. See predictive biomarkers; prognostic biomarkers blinding assay to clinical data, 87, 88 results of interim analyses, 5 bootstrapping, 61, 66, 79 BRB-ArrayTools software, 125 breast cancer enrichment design and trastuzumab, 39 MammaPrint score, 11, 22, 33 Oncotype DX recurrence score, 11, 22-23,35 TAILORx clinical trial, 22-23, 35, 86

139

calibration, 119-120 class comparison, 105-106, 107 class discovery, 105-106 class labels, 107-108, 109, 110, 111 class prediction, 105 bias in estimate of error rates, 111 components of, 107-108 cross-validation, 68, 109-111 leave-one-out-cross-validation, 109-111 definition of, 107-108 estimating accuracy of, 108-112 feature selection, 108, 113-114 mathematical classifier function, 108, 112 - 118classification trees, 117 compound covariate, 70, 116 Fisher discriminant analysis, 115, 116 k-nearest neighbor, 117 nearest centroid classification, 117 nearest neighbor classification, 116, 117-118, 125 support vector machines, 116 weighted voting classifier, 69, 116 misclassification rate, 116, 118 parameter specification, 108 clinical trials. See phase 1 trials; phase 2 trials; phase 3 trials clinical validity, 11, 85 cluster analysis, 106 companion diagnostic, 35-36, 88 Compound Covariate Predictor, 116 confidence interval, 66, 94-95 covariance matrix, 71, 99, 100, 119 Cox's proportional hazard model. See proportional hazards model cross-validated Kaplan-Meier curves, 19f, 121-123, 127 cross-validation, 68, 109-111

adaptive signature design, 75-79 error rate, 110-111 leave-one-out-cross-validation, 109-111 log-rank statistic, 128 10-fold cross-validation, 78 data safety monitoring committee, 5 diagonal linear discriminant analysis, 115-116 enrichment design, 35-43 sample size planning, 42-43 standard design versus, 36-40 test performance/specificity, influence on, 40 trastuzumab study, 39 fall-back analysis, 47-48 false negatives in enrichment designs, 42 in intention to treat analysis, 2 in optimal two-stage design, 26 false positives in gene detection, 12-13 in intention to treat analysis, 2 in optimal two-stage design, 26 feature selection class prediction, 108, 113-114 univariate gene selection, 79 Fisher linear discriminant analysis, 115 futility analysis, interim, 50, 56-57 gene finding, for prognostic classifier, 12-13 Gene Expression Omnibus, 78 gene expression profiles, to develop/validate prognostic classifiers, 105-128 gene shaving, 114

genetic algorithms, 114 genomics, vii, 46, 89 goodness of fit, 13-14 hazard function. See proportional hazards model indication classifier, 46-47 intention to treat, 2 interaction design, 48 interaction tests, 48-49, 54 interim futility analysis, 50, 55-57 intermediate endpoint, 1, 25, 57 k-nearest neighbor classification, 117 Kaplan-Meier survival curves, 14-15, 16f, 18, 96, 121, 125 cross-validated Kaplan-Meier curves, 19f, 121–123, 127 KRAS mutation status, 35, 83, 88 L1 penalized proportional hazards regression, 127 labels, class, 107-108, 109, 110, 111 leave-one-out-cross-validation (LOOCV), 109-111 likelihood full likelihood, 99 maximum, 98, 99 partial, 100 linear discriminant analysis, 115-116 linear regression, 97, 98 LOE (Level of Evidence) Scale, 83 log-rank test, 76-79 cross-validated statistic, 128 logistic regression, 28-29, 99

MammaPrint score, 11, 22, 33 Mann Whitney test, 113 marker strategy design, 21*f*, 20–21 matrix, covariance, 71, 99, 100, 119 maximum likelihood, 98, 99 medical utility, 11, 20, 85 microarray analysis, 78. *See also* prognostic classifiers, based on high dimensional data MINDACT clinical trial, 22–23 misclassification rate, 116, 118 modified marker strategy design, 22*f*, 21–22, 23 molecularly targeted drugs, 1 multicenter clinical trials, 5

nearest centroid classification, 117 nearest neighbor classification, 116, 117–118, 125 nearest shrunken centroid classification, 118–119 noise variables, 108 non-informative prior distributions, 103 nonparametric tests, 93

Oncotype DX recurrence score, 11, 22–23, 35 one-sided p-value, 3 optimal two-stage phase II design, 32–33 over-fitting, 68 p-value, 3 one-sided, 3 two-sided, 3 partial least squares, 114, 120–121

partial likelihood, 100 penalized logistic regression models, 72, 119

permutation test, 65-67, 91-93

phase 2 trials, 25-33 Battle I trial in advanced non-small cell lung cancer, 30-33 Bayesian adaptive designs for randomized phase 2 trials, 30-33 endpoint as progression-free survival, 30 logistic regression analysis, multiple candidate biomarkers, 28-29 predictive biomarker design, single candidate binary, 26-28 predictive biomarkers design, one or more binary candidates, 26 purpose of, 1, 25-26 two-stage design, 26 phase 3 trials endpoint, 2 intention to treat principle, 2 interim analyses, 4-5 overview of, 1-5 pivotal, 36 power, 3-4 purpose of, 45 sample size, 3-4 statistical significance of, 3 subset analyses, 5 population sampling model, 93-94 pre-specified algorithmic analysis plan, 72 predictive biomarkers designs based on single candidate biomarkers, 65-68 designs for development/validation of multivariate classifiers, 68-79 identification and validation of, 35-36 logistic regression model, 28-29 molecularly targeted therapy, 25, 53 multiple, 65-79 one or more binary candidates, 26 predictive classifiers, 68

single candidate, 26-28 and study size, 4 predictive classifiers defining, 35 development of, 106-107 fall-back analysis and, 47-48 indication classifier, 46-48 randomized trial comparing new drug to control regimen, 36 test performance/specificity, influence on enrichment design, 40 predictive pre-specified binary classifier, test positive/test negative patients, 45-57 adaptively modifying types of patients accrued, 55-57 interaction tests, 48-49 probabilistic indication classifier, 49-52 sample size planning, 52-55 probabilistic indication classifier, 49-52 adaptive threshold design and, 60 evaluation of sensitivity/specificity of classifier, 52 probability of early termination (PET), 32t, 33t probabilistic class prediction, 118-120 refinement, 119-120 prognostic biomarkers classification error, 13 false discoveries, 12-13 goodness of fit and, 13-14 medical utility of, 11 sample size, 13 split-sample approach to avoid bias, 14-15. See also prognostic classifiers prognostic classifiers based on high dimensional data, 105-128

combined models, 127-128 evaluating whether, improves on existing prognostic factors, 126-128 marker strategy design, 20–21, 21f medical utility of, 20 modified marker strategy design, 22f, 21-22, 23 univariate gene selection, 79 validation studies of, 20-23 prognostic factor studies, 11 proportional hazards model, 96-97, 99-101, 120 baseline cumulative hazard, 122-123 baseline hazard function, 30, 120 endpoint as progression-free survival, 30 hazard function, 96, 100 hazard ratio, 15 L1 penalized proportional hazards regression, 127 sample size planning, 4 prospective-retrospective design, 83-85 randomization adaptive, 31 Bayesian designs and, 30-33, 49-50 stratified, 30, 45 re-sampling, 14, 125 re-substitution estimate, 111-112 of error rate, 111-112 regression modeling, 11, 97 linear regression, 97, 98 logistic regression, 28-29, 99 proportional hazards regression, 99-101 right-censored data. See survival data ROC (receiver operating characteristic) curve, 124-125

cross-validated ROC, 125

sample size planning, 12-13, 52-55 and adaptive randomization, 31 adaptive threshold design, 62-63 enrichment design, 42-43 optimal two-stage design, 32-33 proportional hazards model, 4 sample splitting, 68 shrunken centroid classification, 117 split-sample method, 109 statistical power, 3-4, 96 statistical significance, 91-94 one-sided p-value, 3 permutation significance test, 65-67 threshold significance level, 4-5, 12, 113 two-sided p-value, 3 stratification design, 45 strong null hypothesis, 59-60, 76 study-wise type I error, 48-49 supervised principle component classifier, 114 support vector machines (SVMs), 116 survival analysis, 96-97 survival risk prediction, 120-125 cross-validated Kaplan-Meier curves, 19f, 121-123, 127 Kaplan-Meier survival curves, 14-15, 16*f*, 18, 96 survival risk classifiers, 120-121 time-dependent receiver operating characteristic curves, 124-125

#### t-test, 113

TAILORx clinical trial, 22–23, 35, 86 threshold significance level, 4–5, 12, 113 time-dependent receiver operating characteristic curves, 124–125 time-to-event endpoint, 54–55, 76–79 tuning parameters, 108 two-way analysis of variance, 48

type I error, 5, 83 in adaptive signature design, 73 and Bayesian methods, 103 defined, 4–5 study-wise, 48–49 two-sided, 12 without specifying cut-point in advance, 60

validity analytical, 11, 88 calibration as measure of, 119–120 clinical, 11, 85 medical utility, 11, 20, 85 of regression model, 101 validation studies of prognostic classifiers, 20–23