Vignette: Application of the RPV method and other functions of the UncertainInterval package

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Abstract

This vignette demonstrates the use of the **UncertainInterval** package for the determination of an interval of uncertain or inconclusive scores of medical tests. It is demonstrated using a large synthetic but realistic data set, with results of the Montreal Cognitive Assessment (MoCA) for the detection of cognitive impairment (CI). It is shown that a more robust result can be expected upon avoiding the range of test scores within which most classification errors are expected, with adequate predictive values for more clinical settings. The clinical settings show sample prevalence's of cognitive impairment that vary widely from .22 to .88. The analysis with the **UncertainInterval** package shows a middle range of test scores that does not differentiate sufficiently between the two true classes of patients. This interval includes a relatively large part of all errors, when compared to an optimal dichotomous threshold that minimizes the sum of errors. Excluding this uncertain or inconclusive range of test scores offers higher classification accuracies for the samples of individual clinical settings. In comparison to a dichotomous threshold, excluding the most error prone test scores enable a classification that offers adequate accuracies in a larger number of clinical settings.

Keywords: threshold determination, uncertain interval, trichotomization, tests, R.

1. Introduction

This paper demonstrates the use of the RPV and other functions of the **UncertainInterval** package for the determination of test scores that are uncertain or inconclusive. This results in three classes: a class of patients with test scores that indicate with a large probability the absence of the targeted impairment, a class of patients with test results that are uncertain or inconclusive, and a class of patients with test scores that most probable indicate the presence of the targeted impairment. This demonstration uses the test scores of the Montreal Cognitive Assessment (MoCA) for the screening of cognitive impairment. The hands-on examples start in paragraph 6.1 and can be applied with version 0.6 or later of the **UncertainInterval** package.

Typically, medical tests are applied to patients who come to a clinical center for their health complaints via referral or by their own choice. In contrast to research samples, these patients are not randomly selected nor can random selection be assumed. Moreover, the population or sub-populations to which they belong can only be defined by thorough investigation of their characteristics. In practice, such research is applied to a part of all patients, a clinical sample that may demonstrate the characteristics of that population.
A medical test is a procedure performed on a patient with a suspected illness to confirm or

determine the presence of the illness. It is relevant for the determination of the targeted disease to know the prevalence or proportion of affected individuals within a population. For the group of patients for whom the disease is suspected, the probability of the disease is often considerably higher than the probability of the disease in the general population. For this reason, the prevalence is often estimated by using the prevalence in the clinical samples of patients, instead of the (much lower) prevalence in the general population. Unsurprisingly, these estimates based on clinical samples can vary widely. The basic question targeted in this paper is how to deal with widely varying estimates of prevalence. The method presented does not solve this problem but enables a classification that offers adequate accuracy in a larger number of clinical settings.

The screening of patients on the possible presence of a disease forms a complicated challenge for both primary care physicians and statisticians. As a running example, data of the Montreal Cognitive Assessment (MoCA) is used. The MoCA (Montreal Cognitive Assessment) is considered as one of the best tests for detection of the possible presence of cognitive impairment in patients. The test has found world-wide application (Freitas, Simões, Alves, and Santana 2013; Larner 2012; Martinelli, Cecato, Bartholomeu, and Montiel 2014). The results of the test may have serious consequences for the patient, even when it is only considered as a first step in the diagnostic process. A false positive may directly lead to cost intensive further testing and may indirectly lead to loss of independence, which may form a frightening perspective for the patient. A false negative may prevent the patient from receiving the help needed to create optimal conditions of life. A decision for or against the presence of cognitive impairment is further complicated as the elderly patient may suffer temporary loss of cognitive abilities due to tiredness, environmental heat, a temporary illness, or the use of drugs for other diseases (Shiota, Torimoto, Momose, Nakamuro, Mochizuki, Kumamoto, Hirayama, and Fujimoto 2014). It is therefore undesirable to jump to conclusions.
The MoCA test is commonly used with a single cutoff score of 26 out of a maximum of 30, with scores 0 to 25 used for a classification of the presence of cognitive impairment and a score of 26 to 30 for the classification of its absence (Nasreddine, Phillips, Bédirian, Charbonneau, Whitehead, Collin, Cummings, and Chertkow 2005). Although this single cutoff score has been challenged by various researchers (Damian, Jacobson, Hentz, Belden, Shill, Sabbagh, Caviness, and Adler 2011; Davis, Creavin, Yip, Noel-Storr, Brayne, and Cullum 2015; Freitas *et al.* 2013), the proposals for alternative cutoff scores remain dichotomized, without considering the possibility of uncertainty in test outcomes.
The model presented here defines three intervals: 1) an interval of uncertain scores where the patients have about equal probability to be classified with the targeted disease or not; 2) a lower range of test scores that indicates the presence of cognitive impairment with high probability; and 3) an upper range of test scores that indicates normal cognitive functioning with high probability. In this way, test scores are trichotomized and interpreted in a way that is straightforward and can be used without much complications in primary care.
On the one hand, this is slightly more complicated than the usual dichotomization methods (Pepe 2003) that are currently applied most frequently for medical decision making, including the determination of possible cognitive impairment. On the other hand, there are far more sophisticated ways to come to individualized predictions (Sheiner and Beal 1982). These methods are often more complicated (Cripps, Wood, Beckmann, Lau, Beckmann, and Cripps 2016), often do not lead to a single and simple interpretable rule (Logan, Sparapani, McCulloch, and Laud 2019) or use a 'black box' prediction model that is difficult to explain to

clinicians (Logan *et al.* 2019). A simpler method may be more practical.
Including the commonly used dichotomization methods, any data-based decision process is a complex form of statistical reasoning, where multiple population estimates are based on the observed individual outcomes of a sample of patients (statistical inference) and then these population estimates are used to interpret the individual patient test score (statistical syllogism). The population estimates assume that the results based on other clinical samples will mirror the results of the sample used in a study.
The basics of the most commonly used method (Receiver Operating Characteristics or ROC) is to consider it as a two-class prediction problem (binary classification) of two samples of patients for whom the true status of their illness is known: a sample of patients selected from the population of patients that are truly affected by the targeted impairment and a sample of patients selected from the population that is not affected (Pepe 2003). The process of selecting the patients from these two populations requires a measurement that is superior to the evaluated medical test, known as a binary gold standard or criterion standard. Subsequently, there are four possible outcomes when a two-class classifier with a single threshold is used. If the outcome from a classification is the possible presence of the disease and the patient is selected form the sample of patients with the illness, this is called a true positive (TP). When the test result points to the absence of the impairment for a patient selected from the sample of patients with the impairment, it is considered a false positive (FP). A true negative (TN) occurs when the classification outcome is the absence of the impairment and the patient is selected from the sample of patients without the impairment, and a false negative (FN) is found when the classification outcome is the absence of the impairment while the patient is selected from the sample of patients that do have the impairment.
The common way to find a suitable dichotomous cutoff score is the use of the receiver operating characteristics of the test, the true positive rate ($TPR = Sensitivity = TP/(TP+FN)$) against the false positive rate ($FPR = 1 - Specificity = 1 - TN/(TN+FP)$), where all possible test scores are considered as possible thresholds to form two classes. The original proposal of Nasreddine et al. (2005) for the dichotomous cutoff score of the MoCA is based on the balance of sensitivity (Se) and specificity (Sp). A more usual solution is the optimization of the sum of Se and Sp, following the proposals of Youden (Youden 1950). This solution also minimizes the sum of the False Positives ($FP = 1 - Sp$) and False Negatives ($FN = 1 - Se$) as it minimizes the proportions of the sum of both type of errors $Max(Se+Sp) = Min(1-Sp+1-Se)$. It is often considered as the optimal threshold. The cutoff score that is defined in this way, is equal to the point of intersection of the densities of the two samples of patients (Schisterman, Perkins, Liu, and Bondell 2005). This is the point where the two samples show no difference in their densities or relative frequencies, and one might say that the optimal threshold is also the point where it is impossible to distinguish the two samples based on the test score alone. In this paper, the optimal threshold is also considered as the test score that offers maximal classification uncertainty.
Many researchers have argued for the allowance of uncertainty when interpreting test outcomes, both in the past (Coste, Jourdain, and Pouchot 2006; Coste and Pouchot 2003; Feinstein 1990; Greiner 1995; Simel, Feussner, Delong, and Matchar 1987) and more recently (Hofmann 2019; Landsheer 2016, 2018; Schuetz, Schlattmann, and Dewey 2012; Shinkins and Perera 2013). However, this has not resulted in a change of preferred methods, and dichotomization using Receiver Operating Characteristics is still the most used methodology.
In this paper, the interval of uncertain test scores is defined as an interval around the point of intersection in which the densities of the two samples of patients with and without the

targeted impairment are about the same. The size of this interval is dependent on the quality of the test (the better the test, the smaller the interval) and the amount of uncertainty that is allowed. The allowable amount of uncertainty is of course a subject for discussion.

2. Data

2.1. Data set

The original data of 5019 patients is part of the Uniform Data Set (UDS), collected by the University of Washington's National Alzheimer's Coordinating Center (NACC) and has been described extensively (Beekly, Ramos, Lee, Deitrich, Jacka, Wu, Hubbard, Koepsell, Morris, and Kukull 2007; Weintraub, Salmon, Mercaldo, Ferris, Graff-Radford, Chui, Cummings, DeCarli, Foster, and Galasko 2009). Results of the original data are available in (Landsheer In press). The results in this paper are based on an anonymised, synthesized data set (synthdata_NACC) that can be published (with the kind permission of the NACC). The MoCA data has been collected in the period from March 2015 to August 2018. The test results of 5531 patients at their first visit are available. Participants were examined in 30 US ADCs. Consent was obtained at each individual ADC. The subject's cognitive status has been determined at every visit: normal cognition (NC), cognitively impaired but not meeting the criteria for MCI, mild cognitive impairment (MCI) and Dementia. The CDR® Dementia Staging Instrument (CDR) was used (Morris 1997; Morris, Ernesto, Schafer, Coats, Leon, Sano, Thal, and Woodbury 1997)) and the global CDR score was calculated using the defined scoring algorithm. This score is useful for characterizing a patient's level of cognitive impairment / dementia, with score 0 indicating normal cognitive functioning.

The original data set is available for researchers from the National Alzheimer's Coordinating Center `https://www.alz.washington.edu/WEB/nacc_handbook.html`. Also, see the acknowledgement at the end of the paper.

2.2. Gold standard

The patients with and without cognitive impairment are defined with their cognitive status and the global CDR at their first visit to the ADC. Following Weintraub et al. (Weintraub, Besser, Dodge, Teylan, Ferris, Goldstein, Giordani, Kramer, Loewenstein, and Marson 2018), the norm group is defined with a cognitive status of Normal Cognition and a global CDR score of 0, while the other patients are defined as having minor or serious cognitive impairment (a cognitive status other than NC and CDR > 0). Patients who have received an ambiguous assessment (CDR > 0 and a cognitive status of NC, or a CDR of 0 and a cognitive status other than NC) have been excluded (n = 512). Participants in the norm group who achieved low scores on the MoCA were not removed from the analyses as the patient's status was not defined by the test. This resulted in a healthy norm group of size 2379 and a group with a varying level of cognitive impairment of 2640, a total of 5019 patients. The prevalence of cognitive impairment is .53.

2.3. Synthesized example data

For use as an example, with kind permission of the NACC, a single data set of 6670 obser-

vations from 30 different clinical centers is generated using the NACC data set as a base. To generate the artificial data, the R package **synthpop** (Nowok, Raab, and Dibben 2016) was used. Results of the real data are available in (Landsheer In press). Clearly, these example data differs from those derived from the true NACC data set. Nevertheless, the statistical results are comparable enough to demonstrate the different methods in the package **UncertainInterval**. This data set is named synthdata_NACC. The data set contains 8 variables: ID, center, ref.1, MOCATOTS.1, vdate.1, ref.2, MOCATOTS.2, and vdate.2, respectively (renumbered) person ID, (renamed) ID of the clinical center, reference measurement of the true presence of cognitive impairment at the first measurement, the MoCA total score at the first measurement, the data of the first measurement, reference measurement of the true presence of cognitive impairment at the second measurement, the MoCA total score at the second measurement and the date of the second measurement. At the first measurement, there are 2433 observations of patients with no clinical assessment of cognitive impairment and 2644 observations with a clinical assessment of some form of cognitive impairment.

Researchers who want to use these data for other purposes than replication of the results presented here, are kindly requested to submit a new request for the original data to the NACC. The user of the data may either get a new file or request a file using the specifications of the original data file (https://www.alz.washington.edu/).

3. The problem of prevalence

The prevalence of a disorder can vary widely between different clinical institutions. In the original NACC data set, prevalence of cognitive impairment varied from .22 to .87 for the different centers. In the total sample, the prevalence was .53. In clinical samples, the patients are not randomly chosen, but arrive at a clinical center by referral or by choice. It is therefore difficult to determine a generally valid estimate of prevalence and clinical samples are difficult to compare with each other.

The optimal cutoff scores for the individual ADCs vary from 19 to 26, with scores smaller or equal to the optimal cutoff score indicating the possible presence of cognitive impairment. The optimal cutoff score for the total sample is 23. When the prevalence is low, the large number of patients without the impairment results in a large number of patients that are erroneously classified positive (false positives). When prevalence is high, a large number of patients with the impairment receives a negative classification (false negatives). Consequently, the patterns of incorrect classification differ widely, are strongly correlated with prevalence and result in a wide variation of negative and positive predictive values (NPV and PPV). The proportion of correctly classified patients can and will vary dramatically between clinical settings with different prevalence. In general, prevalence is strongly positively correlated to the proportion of correctly classified true patients, and negatively correlated with the proportion of correctly classified patients without the impairment. Seemingly, this reflects negatively on the clinical setting, while in reality a relatively large or small proportion of miss-classifications is due to a large or small proportion of patients with the impairment.

Prevalence has no effect on sensitivity and specificity, provided that the two patient samples are drawn from the same populations of patients with and without the targeted condition. This makes sensitivity and specificity excellent markers of the accuracy of the test, allowing for the comparison of different samples with varying prevalence and allowing for comparing different tests using the same sample. It is however problematic that this does not inform us

about the accuracy of the test result for the patients involved. Se and Sp provide information about the proportion of correctly diagnosed patients, *when given knowledge about the true status of the patient*. Obviously, this latter piece of information is not available when a new patient is screened (Gallagher 2003). Despite the prevalence problems mentioned above, a positive or negative predictive value (PPV or NPV) provides a clear interpretation for patients: it indicates the probability of a correct classification, *given the test result* (Gallagher 2003). Predictive values consequently provide information about the accuracy of the classification obtained in the clinical setting.

Ransohoff & Feinstein (1978) have stressed that the problem with prevalence is further complicated due to differences in spectrum bias, when the patients are selected from various (sub)populations with a different mix of patients. In that case, varying values can also be expected for Se and Sp and these values can be dependent on prevalence (Brenner and Gefeller 1997; Usher-Smith, Sharp, and Griffin 2016).

The predictive values (PPV and NPV) provide the proportions of patients classified correctly in the clinical setting and a low proportion may give reason for concern. Fundamentally, this concern can be addressed by using better tests, but these may not be available. The raw classification performance expressed as NPV and PPV at one clinic is not predictive of the classification performance at another and clinics cannot be compared in this way. A proposal to address this comparability problem is to use standardized predictive values that recalculate the predictive values for an assumed prevalence of .5 (Heston 2011, 2014).

It is difficult to estimate prevalence for clinical samples. It is clear that patients being tested for a specific disease are not randomly selected from the general population, but are selected by referral or self-referral. Furthermore, it is unknown from which (sub)population they are selected. Heston (2014) argued that as diagnostic tests are most frequently ordered when the diagnosis is unclear (ie, the pretest likelihood of disease is around 50%), standardizing predictive values to a prevalence of 50% may be more meaningful to the practicing clinician than estimates based on prevalance. When doing so, these standardized estimates ($SNPV$ and $SPPV$) of the predictive values are no more dependent on prevalence than Se and Sp (for dichotomized estimates: $SPPV = Se/(Se + 1 - Sp)$ and $SNPV = Sp/(Sp + 1 - Se)$).

In this paper, another way is proposed to lessen the problem of prevalence. Although it is commonly known that tests offer the best predictions in the tails and predictions for the test scores in the middle are far less predictive, this knowledge is seldom applied when the cutoff scores are determined for the interpretation of the test results. In such a middle range, a relatively high proportion of classification errors can be expected. When such a range of uncertain scores is excluded from a decision for or against the targeted disease, a relatively large number of errors are prevented, and sufficient classification results for the scores outside this range can be found more often.

4. Managing uncertain test scores

There are different ways to help patients with uncertain test scores. The first possibility is to apply further tests to reduce the uncertainty of the classification. This assumes the availability of another tests that offer additional accuracy. A second possibility is to await further developments, either by active surveillance or by watchful waiting (Bangma, Bul, van der Kwast, Pickles, Korfage, Hoeks, Steyerberg, Jenster, Kattan, Bellardita, and al 2013). When a targeted disease is the most serious and the potential consequences of being left

untreated cannot be ignored, while effective treatment has no serious side effects for patients without the targeted disease, it is better to choose treatment even in those cases where the presence of the disease is the most uncertain (Brown and Reeves 2003; Sonis 1999). Treatment possibilities, benefits and costs of treatment for both correctly classified patients and for erroneously classified patients are the more relevant when the classification outcome is uncertain. Knowledge of the inconclusiveness or uncertainty of the test outcomes can be most helpful for many medical decisions.

5. Unstandardized and standardized predictive values

When the classification problem is defined as a selection problem, the basic question is whether a patient is selected from the population of patients with or from the population of patients without the disease. This question cannot be answered for the individual patient, but it is possible to estimate the probabilities for the patients that have obtained a specific test score using Bayesian methods. In the end, the estimates for groups of patients with a given test score are applied to the single patient with the same test score. The probability estimates are derived from multiple population estimates. The desired estimates are undoubtedly better when the samples used for their estimation are larger.

5.1. Predictive values

Predictive values give the probabilities for the presence of the disease, when the obtained test result is known (Gallagher 2003). Predictive values therefore provide information about the accuracy of the classification. Usually the negative predictive value (NPV) is calculated for the dichotomized range of test scores used for a negative classification (test scores > dichotomous cut-point c), leading to the formulation $NPV = TN/(TN + FN)$ and the PPV for positive classifications (the range of test scores <= c; $PPV = TP/(TP + FP)$), where TN, FN, TP and FP concerns the number of respectively true negative, false negative, true positive and false positive observations. A more general definition is needed in the context of three-way classification. Predictive values indicate the likelihood of the patient's negative and positive real status, given the range of test scores x. More generally, predictive values are based on the observed frequencies in the two samples of patients with and without the targeted disease. For a range of test scores x, if $f_0(x)$ and $f_1(x)$ are the frequencies of patients without and with the targeted disease given x, the negative predictive value (NPV) can be defined as: $NPV(x) = f_0(x)/(f_0(x) + f_1(x))$ and the positive predictive value (PPV) as: $PPV(x) = f_1(x)/(f_0(x) + f_1(x))$. This definition also shows that $NPV(x) = 1 - PPV(x)$ when calculated for the same range of test scores x.
These predictive values are exact for the observed patients with and without the targeted disease and are valid for the observed sample prevalence. Interpreting the predictive values of individual test scores is straightforward. For instance, when 240 true patients from a sample have score 25, and 257 patients without the targeted disease have score 25 a patient who receives MoCA test score 25, will consequently have a $240/(240 + 257) = 0.48$ probability to belong to the group with CI. This number is exact for the sample involved. These predictive values therefore indicate the accuracies of the classifications in the sample, given the range of applied test score(s). As such, it is an important outcome for evaluating the accuracy of classification in a sample, given the observed test score(s). For comparisons of methods, this

paper considers the values of .8 or higher as sufficient, both for NPV and PPV.

5.2. Standardized predictive values.

Heston's proposal (2011; 2014) to standardize predictive values was made in the context of a single cut-point. However, it makes sense to also use a more general definition here, and to relate standardized predictive values to the relative frequencies or densities of the (range of) test score(s). The densities for a range of test scores x can be defined $d_0(x) = f_0(x)/n_0$ and $d_1(x) = f_1(x)/n_1$, where n_0 and n_1 are the number of observed patients in the two samples. The standardized negative predictive value ($SNPV$) is defined as $SNPV(x) = d_0(x)/(d_0(x)+d_1(x))$ and the standardized positive predictive value ($SPPV$) as $SPPV(x) = d_1(x)/(d_0(x) + d_1(x))$. The two distributions are weighted equally, or in other words, the prevalence is standardized to .5. The interpretation of the standardized predictive values is not as straightforward as the interpretation of the common predictive values: they provide the estimated relative probability which of the two distributions makes the observed test score most likely, the distribution of the population of patients with or the population without the disease. If, for instance, 8% of true patients have score 25, and 11% of patients without CI have score 25, a patient with test score 25 has an estimated relative probability of $8/(8+11) = 0.42$ to belong to the population with cognitive impairment and a probability of 0.58 to belong to the population without cognitive impairment. The estimates improve with larger samples. Standardized predictive values can be used to identify the range of uncertain test scores that offer a limited distinction between the populations of patients with and without the targeted disease. It should also be noted that the predictive values of two samples of patients with and without the targeted impairment (PPV and NPV) can be different from the estimates of the standardized predictive values for the two populations ($SPPV$ and $SNPV$). These differences are more substantial when prevalence deviates more strongly from .5.

5.3. Post-test probabilities.

Posttest probabilities (Sonis 1999) may seem quite different from predictive values, but they are not. The posttest probability is equal to the positive predictive value when the pretest probability is set to the sample prevalence, while the standardized positive predictive value is equal to the posttest probability when the pretest probability is set to .5. Post-test probabilities are most versatile, as they can be calculated for every possible value of prevalence. However, it is difficult to choose a 'correct' prevalence for a patient for whom the presence of the targeted impairment is unknown, and an assumed pre-test probability of 0.5 is often the most reasonable. (It should be noted that Sonis (1999) discusses a serious disease with low prevalence for which a relatively harmless and effective cure exists. It should be clear that in such a case a decision to apply the cure is easily made, even when the positive test outcome has low probability and the true presence of the disease is most uncertain.)

5.4. Uncertain test scores.

This is defined as a range of test scores with about equal densities in the two distributions of patients with and without the targeted disease. Standardized predictive values are therefore most suited to the determination of this range of uncertain test scores. How much uncertainty can be allowed is open for discussion. This paper uses an $SNPV$ and an $SPPV < .667$ (odds

of NCI and CI two to one or less) to define test scores that are too uncertain for classification concerning the presence of CI.

5.5. Test reliability and smoothing.

Even if all circumstances remain the same, we cannot expect to find the same test score for a patient when the same test is taken a second time. Due to random influences, a second test score will be slightly lower or higher. Reliable estimates of these predictive probabilities are consequently needed, and these should be corrected for this randomness to a certain degree. In test theory, this random effect is estimated with the Standard Error of Measurement (SEM), which depends directly on the reliability of the test: $SEM = s\sqrt{1-r}$, where s is the standard deviation of the test scores and r the estimated reliability of the test (Crocker and Algina 1986; Harvill 1991). The true score of an individual patient lies with some probability (roughly 68%) within a range of ± 1 SEM around the observed test score. This provides information about the range of test scores where the true score of the patient can be expected. The average standardized predictive values of a fixed number of consecutive test scores (in this case 5) are calculated, where each subset of test scores is modified by a forward shift, excluding the first test score and including the next test score. Such a moving average smooths the predictive values, stabilizes the estimates across different samples, and mitigates peculiarities in the sample. For the determination of thresholds, standardized predictive values are calculated for the range of ± 1 SEM around each test score to obtain more stable predictive values.

6. Determination of an uncertain interval

The **UncertainInterval** package has been developed over several years (Landsheer 2016, 2018). Central to all functions developed for the determination of the uncertain interval is that in this interval the density is about equal for patients with and without the targeted disorder. The uncertain interval is located around the point of intersection of the two density distributions. Such an uncertain interval is related to the optimal dichotomous threshold where the sum of the error probabilities ($1 - Sp + 1 - Se$) are minimized, which is the same threshold where the sum $Se + Sp$ is maximized (Youden 1950).

The first developed function is `ui.nonpar` for the non-parametric determination of an uncertain interval around the point of intersection that can be applied to continuous test scores. It iteratively searches for an interval of test scores around the point of intersection where these isolated test scores have a given value for both Se and Sp (the default value is .55). Simulation results and an application to a clinical example are published in Landsheer (2016). The clinical example concerns the prediction of the severity of prostate cancer and is applied to data published by Hosmer and Lemeshow (2000). As Se and Sp have been developed as the characteristics of dichotomization of the full range of observed test scores, the use of Se and Sp as quality indices for limited ranges of test scores may be counter-intuitive. Commonly used functions for the calculation of Se and Sp do so for the full range of observed test scores. Therefore, the functions `quality.threshold.uncertain` and `quality.threshold` have been created. The function `quality.threshold.uncertain` calculates quality indices for the range of test scores that form the uncertain interval. When two thresholds are provided, the function `quality.threshold` calculates the quality indices for the test scores outside the uncertain interval, ignoring the test scores in the uncertain interval in between the two thresholds. The

functions can also be used for the more usual calculation of quality indices of the test when applying a single threshold. The function `ui.binormal` is used for the determination of an uncertain interval when the two distributions of test scores are assumed to follow a bi-normal distribution. Instead of a search routine, the function uses an optimization algorithm from the nlopt library https://nlopt.readthedocs.io/en/latest/NLopt_Algorithms/: the sequential quadratic programming (SQP) algorithm for non-linearly constrained gradient-based optimization (supporting both inequality and equality constraints), based on the implementation by Kraft (1988; 1994). In Landsheer (2018) simulation results are published, while the capabilities of the trichotomization method are demonstrated on an empirical data set published in Andrews and Herzberg (1985) and available in the R package **ipred** (Peters, Hothorn, Ripley, Therneau, and Atkinson 2015). The data set concerns observations of 75 female Duchenne muscular dystrophy (DMD) carriers and 134 female DMD non-carriers. The various methods are demonstrated for the serum creatine kinase (CK), marker for the determination of DMD carriers. The CK marker offers a concordance (AUC or C-statistic) of 0.87. The CK-marker is not the best marker for this determination but enables the demonstration of the `ui.binormal` method. Later, this function was generalized to cover a wider variety of distributions different from the bi-normal distribution (function `nl.opt.general`).
For comparison, the TG-ROC method of Greiner (1995; 1996) and the Grey-zone method of Coste et al. (2006; 2003) have been used in the two publications (Landsheer 2016, 2018). As the software for these methods is not generally available, two functions (`TG.ROC` and `greyzone`) have been added to the **UncertainInterval** package from version 0.5 onwards. These two methods are also trichotomization methods but differ from the **UncertainInterval** methods. Both methods are based on dichotomous operation characteristics for all possible cutoff-scores of the test. The resulting middle section of the trichotomization (called intermediate or grey-zone) often overlaps the interval of uncertain test scores but is not necessarily related to the optimal dichotomous cutoff score or to equality of densities and can have different properties. These differences are discussed in Landsheer (2018).

As tests often have discrete scores of interval level, a function has been added for the exploration of possible uncertain intervals of ordinal test results (`ui.ordinal`). This function can be applied to small samples of tests with a limited number of ordinal outcomes but as such it is intended for exploration. Preferably, the determination of cutoff scores intended for general use should be based on large samples. When the number of discrete scores is small, Se and Sp of a middle section can vary greatly and a specific value such as the default value of Se and Sp of .55 may be hard to obtain. The `ui.ordinal` function therefore allows for multiple criteria that can be used for the determination of an inconclusive middle section.
The ideas presented by Sonis (1999) and others (Brown and Reeves 2003; Gallagher 1998) about interval likelihood ratios, showed that predictive values, standardized predictive values, post-test probabilities, as well as interval likelihood ratios can be used in a straightforward manner for the determination of the quality indices of intervals of test scores. The existence of large clinical data sets such as the NACC data set enables the calculation of these indices for small ranges of test scores, even when the interval is as small as a single test score. This has resulted in the `RPV` function of the **UncertainInterval** package, which calculates predictive values, standardized predictive values, interval likelihood ratios and posttest probabilities of intervals of test scores or even the individual test scores of discrete ordinal tests.
This paper limits itself to the demonstration of the `RPV` function and several help-functions that are part of the **UncertainInterval** package. For the explanation and demonstration of the

other functions see (Landsheer 2016, 2018) and their supplemental files and the other vignette in the **UncertainInterval** package.

6.1. Exploring the problem

The first step in the analysis of bi-distributed test scores is the plot of the distributions. First, we select the first measurements and then plot these distributions. The **UncertainInterval** package has two functions for the purpose: `plotMD` and `barplotMD`. Both can be used for ordinal data, but `plotMD` is more useful when data are continuous. The following code loads the package and the example data set and shows the head and the total number of observations of the data set.

```
R> library(UncertainInterval)
R> packageVersion("UncertainInterval") # should be 0.6.0 or later

[1] '0.6.0'

R> data('synthdata_NACC')
R> head(synthdata_NACC)

     ID center ref.1 MOCATOTS.1 vdate.1 ref.2 MOCATOTS.2 vdate.2
14 6411     AD     1          7   16981    NA         NA      NA
36 1079      H     1         21   17095    NA         NA      NA
51 4012      W     0         25   17323    NA         NA      NA
52  785      C    NA         28   17415    NA         NA      NA
70  887      Y    NA         NA      NA     1         22   16772
73 3292      P     1          2   16997    NA         NA      NA

R> nrow(synthdata_NACC)

[1] 6670
```

Next, we select the part of data with the first measurements. The gold standard is defined by two variables (see paragraph 2.2). These two variables can result in an inconclusive gold standard, which are excluded:

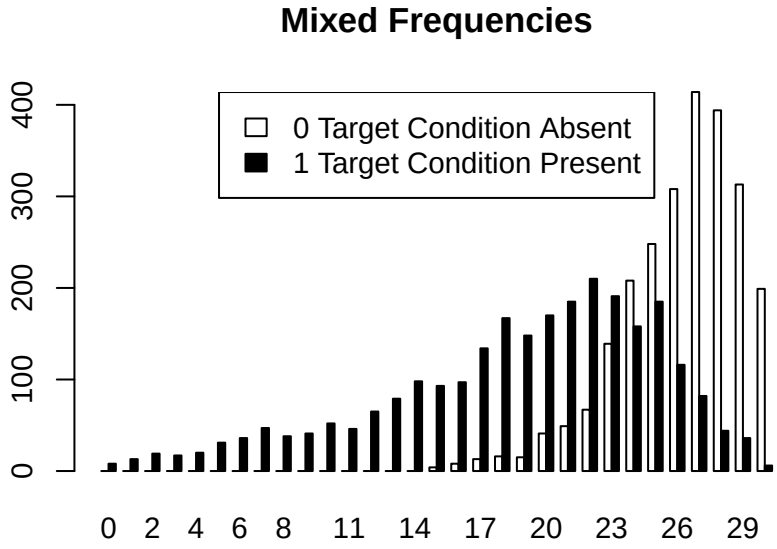
```
R> m1 = synthdata_NACC[!is.na(synthdata_NACC$MOCATOTS.1) &
R+                       !is.na(synthdata_NACC$ref.1), ]
```

Next, check the data for possible missing values and plot the data when everything is ok:

```
R> addmargins(table(m1$ref.1, m1$MOCATOTS.1, useNA = 'always'))

     0  1  2  3  4  5  6  7  8  9 10 11 12
  0  0  0  0  0  0  0  0  0  0  0  0  0  0
```

```
  1        8   13   19   17   20   31   36   47   38   41   52   46   65
  <NA>     0    0    0    0    0    0    0    0    0    0    0    0    0
  Sum      8   13   19   17   20   31   36   47   38   41   52   46   65

           13   14   15   16   17   18   19   20   21   22   23   24   25
  0         0    0    4    8   13   16   15   41   49   67  139  208  248
  1        79   98   93   97  134  167  148  170  185  210  191  158  185
  <NA>      0    0    0    0    0    0    0    0    0    0    0    0    0
  Sum      79   98   97  105  147  183  163  211  234  277  330  366  433

           26   27   28   29   30 <NA>  Sum
  0       308  414  394  313  199    0 2436
  1       116   82   44   36    6    0 2632
  <NA>      0    0    0    0    0    0    0
  Sum     424  496  438  349  205    0 5068
```

```
R> barplotMD(m1$ref.1, m1$MOCATOTS.1)
```



The bar plot of these realistically simulated data shows the observations of 2436 patients with no cognitive impairment and 2632 patients with cognitive impairment.

It is easy to see that distinguishing patients with and without cognitive impairment based on the MoCA test score is relatively easy at the low end of the test scores: at the low end patients without cognitive impairment are hardly present. Distinction at the high end of the test scores is more difficult, as both patients with and without cognitive impairment can perform quite well on the test and obtain relatively high test scores.

As most functions in the **UncertainInterval** package assume higher scores for patients with

the targeted condition, the data need to be negated. This is also the case for the quality functions. When applying the commonly used cutoff score of 25, with test score 25 and lower indicating the presence of cognitive impairment, the following results are obtained.

```
R> quality.threshold(m1$ref.1, -m1$MOCATOTS.1, threshold = -25)

$table
                       ref
y.hat                    0    1  Sum
  0 (test < threshold)  1628  284 1912
  1 (test >= threshold)  808 2348 3156
  Sum                   2436 2632 5068

$cut
threshold
      -25

$indices
Proportion.True             CCR         balance              Sp
      0.5193370       0.7845304       3.6410256       0.6683087
              Se             NPV             PPV            SNPV
      0.8920973       0.8514644       0.7439797       0.8609880
            SPPV             LR-             LR+               C
      0.2710364       0.1614564       2.6895408       0.8866365
```

The negation of the test scores only influences the table, as the correct interpretation of the table needs the reversal of the inequalities: 0 (test score > threshold of 25) and 1 (test score <= 25). The concordance (or AUC) is .89. The Area under the Curve (AUC) is indicated as concordance in the **UncertainInterval** package, as AUC sometimes leads to confusion about which curve is meant. The correct name is Area under the Receiver Operating Characteristics Curve or AUROCC. When every possible pair is formed with one observation from the sample with the disease and one from the sample of patients without the disease, the AUROCC statistic is also the concordance between test result and gold standard. The concordance is the probability that the model correctly ranks all possible pairs of observations. The name "concordance" or C-statistic for this statistic is therefore also applicable.
Although the choice of the creators of the MoCA for this cutoff score of 25 was based on a balance between Se and Sp, this balance is not obtained in this clinical sample. The specificity of .67 is quite low. The optimal Youden threshold is 23 with scores <= 23 indicating Cognitive Impairment. This agrees with the estimated point of intersection (test scores <= 23.54 indicate CI equally well):

```
R> get.intersection(m1$ref.1, -m1$MOCATOTS.1)

[1] -23.53688
```

As the Youden threshold maximizes the sum of $Se + Sp$, the results are slightly better than when using 25 as a threshold:

```
R> quality.threshold(m1$ref.1, -m1$MOCATOTS.1, threshold = -23)

$table
                       ref
y.hat                    0    1  Sum
  0 (test < threshold)  2084  627 2711
  1 (test >= threshold)  352 2005 2357
  Sum                   2436 2632 5068

$cut
threshold
      -23

$indices
Proportion.True             CCR         balance              Sp
      0.5193370       0.8068272       4.1767109       0.8555008
              Se             NPV             PPV            SNPV
      0.7617781       0.7687200       0.8506576       0.7821917
            SPPV             LR-             LR+               C
      0.1594426       0.2784590       5.2718508       0.8866365
```

Next, we explore the prevalence of the different centers:

```
R> t = addmargins(table(m1$ref.1, m1$center, useNA = 'always'))
R> t = rbind(t, t[2,]/(t[2,]+t[1,]))
R> to = t[,c(order(t[5,1:30]),31:32)]
R> rownames(to) = c('0', '1','<NA>','Sum', 'prev')
R> round(to, 3)

           Q       W      AA       Z       O       L       I       D
0    218.000  89.000 149.000  93.000  89.000 138.000 260.000 119.000
1     60.000  30.000  54.000  34.000  34.000  55.000 112.000  57.000
<NA>   0.000   0.000   0.000   0.000   0.000   0.000   0.000   0.000
Sum  278.000 119.000 203.000 127.000 123.000 193.000 372.000 176.000
prev   0.216   0.252   0.266   0.268   0.276   0.285   0.301   0.324
           X       A      G     AB       M       T       J      R      V
0    114.000  75.000 169.00 55.000 108.000  81.000  90.000 41.000 31.000
1     56.000  42.000 108.00 39.000  84.000  74.000  87.000 46.000 36.000
<NA>   0.000   0.000   0.00  0.000   0.000   0.000   0.000  0.000  0.000
Sum  170.000 117.000 277.00 94.000 192.000 155.000 177.000 87.000 67.000
prev   0.329   0.359   0.39  0.415   0.438   0.477   0.492  0.529  0.537
          P      N       U      AC      F       Y      H       C       E
0    13.000 31.000 105.000  65.000 27.000  40.000  33.00  41.000  34.000
1    16.000 48.000 176.000 123.000 65.000 116.000  99.00 135.000 122.000
<NA>  0.000  0.000   0.000   0.000  0.000   0.000   0.00   0.000   0.000
Sum  29.000 79.000 281.000 188.000 92.000 156.000 132.00 176.000 156.000
prev  0.552  0.608   0.626   0.654  0.707   0.744   0.75   0.767   0.782
```

```
           K      AD       S      B <NA>      Sum
0     55.000  50.000  18.000  5.000    0 2436.000
1    284.000 288.000 114.000 38.000    0 2632.000
<NA>   0.000   0.000   0.000  0.000    0    0.000
Sum  339.000 338.000 132.000 43.000    0 5068.000
prev   0.838   0.852   0.864  0.884  NaN    0.519
```

```
R> center = colnames(to)[1:30] # sorted on sample prevalence
```

The overall prevalence for this sample is .52, but it varies for the individual centers in this synthesized sample from .22 to .88. Now we obtain the test indices for the individual centers when the optimal threshold is applied:

```
R> indm = matrix(NA, 30, 9)
R> yt = rep(NA, 30)
R> for (i in 1:30) {
R+   # i=1
R+   ref = m1[m1$center == center[i], ]$ref.1
R+   unique(ref)
R+   test = -m1[m1$center == center[i], ]$MOCATOTS.1
R+   N0 = length(test[ref == 0])
R+   N1 = length(test[ref == 1])
R+   indm[i, ] = c(N0, N1,
R+                 quality.threshold(ref, test, threshold = -23,
R+                    model = 'ordinal')$indices[c(1, 4:9)])
R+ }
R> colnames(indm) = c('n0', 'n1', 'prev', 'Sp', 'Se', 'NPV', 'PPV', 'SNPV', 'SPPV')
R> rownames(indm) = 1:30
R> round(indm, 3)
```

```
    n0  n1  prev    Sp    Se   NPV   PPV  SNPV  SPPV
1  218  60 0.216 0.899 0.967 0.990 0.725 0.964 0.095
2   89  30 0.252 0.798 0.500 0.826 0.455 0.615 0.288
3  149  54 0.266 0.852 0.889 0.955 0.686 0.885 0.142
4   93  34 0.268 0.849 0.794 0.919 0.659 0.805 0.159
5   89  34 0.276 0.910 0.824 0.931 0.778 0.838 0.098
6  138  55 0.285 0.964 0.655 0.875 0.878 0.736 0.052
7  260 112 0.301 0.888 0.759 0.895 0.746 0.787 0.128
8  119  57 0.324 0.706 0.860 0.913 0.583 0.834 0.255
9  114  56 0.329 0.868 0.768 0.884 0.741 0.789 0.146
10  75  42 0.359 0.867 0.357 0.707 0.600 0.574 0.272
11 169 108 0.390 0.734 0.741 0.816 0.640 0.739 0.264
12  55  39 0.415 1.000 0.385 0.696 1.000 0.619 0.000
13 108  84 0.438 0.759 0.714 0.774 0.698 0.727 0.252
14  81  74 0.477 0.741 0.865 0.857 0.753 0.846 0.231
15  90  87 0.492 0.900 0.805 0.827 0.886 0.822 0.111
16  41  46 0.529 1.000 0.652 0.719 1.000 0.742 0.000
```

```
17  31  36 0.537 0.903 0.500 0.609 0.857 0.644 0.162
18  13  16 0.552 0.538 0.938 0.875 0.714 0.896 0.330
19  31  48 0.608 0.806 0.771 0.694 0.860 0.779 0.201
20 105 176 0.626 0.781 0.835 0.739 0.865 0.826 0.208
21  65 123 0.654 0.877 0.829 0.731 0.927 0.837 0.129
22  27  65 0.707 0.778 0.769 0.583 0.893 0.771 0.224
23  40 116 0.744 0.925 0.767 0.578 0.967 0.799 0.089
24  33  99 0.750 0.909 0.747 0.545 0.961 0.783 0.108
25  41 135 0.767 0.976 0.593 0.421 0.988 0.705 0.040
26  34 122 0.782 0.824 0.910 0.718 0.949 0.901 0.162
27  55 284 0.838 0.909 0.761 0.424 0.977 0.792 0.107
28  50 288 0.852 1.000 0.851 0.538 1.000 0.870 0.000
29  18 114 0.864 0.833 0.693 0.300 0.963 0.731 0.194
30   5  38 0.884 1.000 0.500 0.208 1.000 0.667 0.000
```

The centers are sorted on the prevalence of CI found in their data. The following matrix shows the correlations between prevalence and the various quality indices:

```
R> round(cor(indm[,'prev'], indm[,c('NPV', 'PPV', 'Sp', 'Se', 'SNPV', 'SPPV')]), 2)

       NPV  PPV   Sp    Se SNPV  SPPV
[1,] -0.87 0.77 0.19 -0.01    0 -0.26
```

The correlations between prevalence and Sp and Se are low. As expected, the correlations between prevalence and NPV and PPV are considerable (-.87 and .77), while the correlations with their standardized version $SNPV$ and $SPPV$ are about as low as the correlations with Sp and Se.

The MoCA has inadequate test accuracy indices (Se and Sp) for some of the centers. The following command line shows the line numbers in table `indm`:

```
R> which(indm[,'Se'] < .7)

 2  6 10 12 16 17 25 29 30
 2  6 10 12 16 17 25 29 30

R> which(indm[,'Sp'] < .7)

18
18
```

It is noteworthy that low sensitivity is found both for centers with low prevalence and for centers with high prevalence of CI. The low Specificity results occur for an center with a prevalence of .552. Clearly, the MoCA does not function equally well for all centers and this should receive more attention (it should be noted that similar results are also obtained for the real data).

Dependent on prevalence, the percentages of correctly classified patients can be quite low. When a lower limit of .8 is used (4 out of 5 patients classified correctly), mainly centers with low prevalence show sufficient values for NPV, while mainly centers with high prevalence show sufficient values for PPV.

```
R> which(indm[,'NPV'] >= .8)

 1  2  3  4  5  6  7  8  9 11 14 15 18
 1  2  3  4  5  6  7  8  9 11 14 15 18

R> which(indm[,'PPV'] >= .8)

 6 12 15 16 17 19 20 21 22 23 24 25 26 27 28 29 30
 6 12 15 16 17 19 20 21 22 23 24 25 26 27 28 29 30

R> which(indm[,'PPV'] >= .8 & indm[,'NPV'] >= .8)

 6 15
 6 15
```

Only for 2 centers, both the value for NPV and PPV are >= .8.

6.2. Determination of an uncertain interval

As explained earlier, we first need the test reliability to enable smoothing of the distributions and obtaining more stable estimates. The time `ddiff` between measurements varies widely. The reliability is estimated with the `ICC` function of the **psych** package.

```
R> ddiff = (m1$vdate.2 - m1$vdate.1)
R> summary(ddiff)

   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.    NA's
   62.0   363.0   385.0   423.3   455.0  1063.0    3192

R> library(psych)
R> ICC(na.omit(cbind(m1$MOCATOTS.1, m1$MOCATOTS.2)))

Registered S3 methods overwritten by 'lme4':
  method                          from
  cooks.distance.influence.merMod car
  influence.merMod                car
  dfbeta.influence.merMod         car
  dfbetas.influence.merMod        car
```

```
Call: ICC(x = na.omit(cbind(m1$MOCATOTS.1, m1$MOCATOTS.2)))

Intraclass correlation coefficients
                         type  ICC  F  df1  df2 p lower bound upper bound
Single_raters_absolute   ICC1 0.86 14 1875 1876 0        0.85        0.87
Single_random_raters     ICC2 0.86 14 1875 1875 0        0.84        0.88
Single_fixed_raters      ICC3 0.87 14 1875 1875 0        0.86        0.88
Average_raters_absolute ICC1k 0.93 14 1875 1876 0        0.92        0.93
Average_random_raters   ICC2k 0.93 14 1875 1875 0        0.91        0.94
Average_fixed_raters    ICC3k 0.93 14 1875 1875 0        0.92        0.94

 Number of subjects = 1876     Number of Judges =  2
```

Over all, `ICC` is .86 for the subjects that have two measurements. The intended distance between the meausurements of the UDS is one year apart. When selecting the patients whose second measurements are between 11 and 13 months apart (335 and 395 days apart), 917 observations remain:

```
R> timesel = (ddiff >= 335) & (ddiff <= 395)
R> ICC(na.omit(cbind(m1$MOCATOTS.1[timesel], m1$MOCATOTS.2[timesel])))

Call: ICC(x = na.omit(cbind(m1$MOCATOTS.1[timesel], m1$MOCATOTS.2[timesel])))

Intraclass correlation coefficients
                         type  ICC  F df1 df2        p lower bound
Single_raters_absolute   ICC1 0.87 15 916 917 1.4e-287        0.86
Single_random_raters     ICC2 0.87 15 916 916 8.2e-292        0.85
Single_fixed_raters      ICC3 0.88 15 916 916 8.2e-292        0.86
Average_raters_absolute ICC1k 0.93 15 916 917 1.4e-287        0.92
Average_random_raters   ICC2k 0.93 15 916 916 8.2e-292        0.92
Average_fixed_raters    ICC3k 0.93 15 916 916 8.2e-292        0.92
                        upper bound
Single_raters_absolute         0.89
Single_random_raters           0.89
Single_fixed_raters            0.89
Average_raters_absolute        0.94
Average_random_raters          0.94
Average_fixed_raters           0.94

 Number of subjects = 917     Number of Judges =  2

R> # ICC(na.omit(cbind(m1$MOCATOTS.1[timesel], m1$MOCATOTS.2[timesel])), lmer=FALSE)
```

The lower estimate (.86) is chosen as the reliability estimate. The `RPV` function calculates predictive values, interval likelihood ratios and post-test probabilities of individual test scores for discrete ordinal tests. The function also trichotomizes the test results, with an uncertain

interval where the test scores do not allow for an adequate distinction between the two groups of patients. To reduce random effects, the standardized predictive values are calculated for a range of scores around the obtained score. As the default calculated range of scores is uneven, the function returns an error and proposes suitable values for the parameter `roll.length` that determines the ranges of test scores. In the following command, `roll.length` is set to 5.

```
R> RPV(m1$ref.1, m1$MOCATOTS.1, reliability = .86, roll.length = 5)

$parameters
     pretest.prob sample.prevalence       reliability               SEM
             0.52              0.52              0.86              2.31
      roll.length    rel.conf.level     decision.odds             limit
             5.00              0.61              2.00              0.67

$messages
     [,1]
[1,] "Reliable Predictive Values for scores  0 1 29 30  have been extended."
[2,] "Decision use = standardized.pv."

$rel.pred.values
           0   1   2   3   4   5   6   7   8   9  10  11  12    13    14
rnpv       0   0   0   0   0   0   0   0   0   0   0   0   0  0.01  0.03
rppv       1   1   1   1   1   1   1   1   1   1   1   1   1  0.99  0.97
rsnpv      0   0   0   0   0   0   0   0   0   0   0   0   0  0.01  0.03
rsppv      1   1   1   1   1   1   1   1   1   1   1   1   1  0.99  0.97
rilr     Inf Inf Inf Inf Inf Inf Inf Inf Inf Inf Inf Inf Inf 88.16 33.32
rpt.odds Inf Inf Inf Inf Inf Inf Inf Inf Inf Inf Inf Inf Inf 95.25 36.00
rpt.prob   1   1   1   1   1   1   1   1   1   1   1   1   1  0.99  0.97
            15    16    17   18   19   20   21   22   23   24   25   26
rnpv      0.05  0.07  0.08 0.11 0.14 0.18 0.26 0.36 0.43 0.53 0.64 0.73
rppv      0.95  0.93  0.92 0.89 0.86 0.82 0.74 0.64 0.57 0.47 0.36 0.27
rsnpv     0.05  0.07  0.09 0.12 0.15 0.19 0.27 0.37 0.45 0.55 0.66 0.74
rsppv     0.95  0.93  0.91 0.88 0.85 0.81 0.73 0.63 0.55 0.45 0.34 0.26
rilr     18.55 13.30 10.56 7.13 5.55 4.33 2.69 1.68 1.21 0.82 0.51 0.34
rpt.odds 20.04 14.37 11.41 7.70 6.00 4.68 2.91 1.81 1.31 0.89 0.56 0.37
rpt.prob  0.95  0.93  0.92 0.89 0.86 0.82 0.74 0.64 0.57 0.47 0.36 0.27
           27   28   29   30
rnpv     0.78 0.85 0.85 0.85
rppv     0.22 0.15 0.15 0.15
rsnpv    0.80 0.86 0.86 0.86
rsppv    0.20 0.14 0.14 0.14
rilr     0.26 0.16 0.16 0.16
rpt.odds 0.28 0.17 0.17 0.17
rpt.prob 0.22 0.15 0.15 0.15

$thresholds.UI
```

```
 L  U
22 25

$ranges
Negative Decisions          Uncertain Positive Decisions
        "26 to 30"         "22 to 25"          "0 to 21"

$results
                  Negative.Decisions Uncertain Positive.Decisions
n                               1912      1406               1750
total.sample                  37.73%    27.74%             34.53%
correct.decisions             85.15%      <NA>             91.66%
true.neg.status               66.83%    27.18%              5.99%
true.pos.status               10.79%    28.27%             60.94%
realized.odds                  5.73      1.12               10.99
```

The parameters of the analysis are presented in `$parameters`. The size of this range is set to (approximate) the score ± 1 SEM. The estimate of SEM is 2.305. The selected `roll.length = 5` sets the ranges of the test score $\pm$ 2 and the results are the moving averages of the test scores $\pm$ 2. This covers a confidence level of 61.4% for the expected true test score. The calculated results are the moving averages over these ranges. Applying the odds of a correct classification as 2 against 1 means the lower limit of $SNPV$ or $SPPV$ is .667 and test scores that offer either an $SNPV$ or $SPPV$ lower than .667 are considered as inconclusive or uncertain.

Reliable standardized predictive values cannot be calculated for the most extreme values (test scores 0, 1, 29 and 30) and are consequently extended from the nearest calculable value. This is reported in `$messages`. The test scores at the extremes of the test results represent the highest and lowest standardized predictive values. In practice, this extension should therefore rarely pose a problem for the determination of the most uncertain test scores, as classification errors are typically found around the Youden threshold (in this case 23) and not in the tails of the distributions.

Various statistics are shown in `$rel.pred.values`. It shows the smoothed predictive values (`rnpv` and `rppv`), the density based standardized negative and positive predictive values (`rsnpv` and `rsppv`), the interval likelihood ratios (`rilnr`), the posttest odds (`rpt.odds`) and the posttest probabilities (`rpt.prob`). In this case, `rpt.prob` equals `rppv` as the prevalence is kept equal to the sample prevalence.

The standardized negative and positive predictive values are used for the decision thresholds. In this case, `rpt.prob` equals `rppv` as the prevalence is kept equal to the sample prevalence as a default. The standardized predictive values are equal to the posttest probabilities when prevalence is set to .5. The decision results are shown in `$result`. The determined uncertain interval is 22 to 25, which contains 27.2% of patients with a true negative status and 28.3% of the patients with a true positive status. The realized decision odds for the uncertain interval are 1.124 which means that the ratio of the densities of patients with and without cognitive impairment $d_1(x)/d_0(x)$ is close to 1. The range 26-30 is selected for negative decisions which results in 85.1% correct decisions and covers 66.8% of the patients with a true negative status. The range 0-21 is selected for positive decisions. It has a percentage of 91.7 of correct decisions and covers 60.9% patients with a true positive status.

Although the uncertain interval contains 27.7% of the total sample, no less than 56% of all errors are found here when the optimal threshold (23) would have been applied:

```
R> class23 = as.numeric(m1$MOCATOTS.1 <= 23)
R> all.err = m1$ref.1 != class23 # errors when using the optimal cut-point
R> sum(all.err[m1$MOCATOTS.1 >= 22 & m1$MOCATOTS.1 <= 25])/ sum(all.err)
```

```
[1] 0.5607763
```

The results of this trichotomization for the individual centers are:

```
R> indm2 = matrix(NA, 30, 9); i=1
R> for (i in 1:30) {
R+   ref = m1[m1$center == center[i], ]$ref.1
R+   test = m1[m1$center == center[i], ]$MOCATOTS.1 # reversed order
R+   # works only correctle with package version >= 0.6.0
R+   res = RPV(
R+     ref,
R+     test,
R+     pretest.prob = .53,
R+     reliability = .86,
R+     roll.length = 5,
R+     decision.odds = 2,
R+     preselected.thresholds = c(25, 22),
R+     use.perc = F
R+   )
R+   indm2[i, ] = c(t(res$res[3:5, ]))
R+ }
R> indm2=cbind(to['prev',1:30], indm2[,c(1,3,4,9,7,6)])
R> colnames(indm2) = c('prev', 'NPV', 'PPV', 'TNR', 'TPR', 'FNR', 'FPR')
R> # Please note: SPPV != Se / (Se + 1 - Sp) and SNPV != Sp / (Sp + 1 - Se)).
R> SNPV = indm2[,'TNR']/(indm2[,'TNR']+ indm2[,'FNR'])
R> SPPV = indm2[,'TPR']/(indm2[,'TPR']+ indm2[,'FPR'])
R> rownames(indm2)= 1:30
R> indm2 = cbind(indm2, SNPV, SPPV)
R> round(indm2, 3)
```

```
    prev   NPV   PPV   TNR   TPR   FNR   FPR  SNPV  SPPV
1  0.216 1.000 0.833 0.711 0.750 0.000 0.041 1.000 0.948
2  0.252 0.919 0.478 0.640 0.367 0.167 0.135 0.794 0.731
3  0.266 0.940 0.860 0.631 0.685 0.111 0.040 0.850 0.944
4  0.268 0.969 0.893 0.667 0.735 0.059 0.032 0.919 0.958
5  0.276 0.950 0.958 0.640 0.676 0.088 0.011 0.879 0.984
6  0.285 0.927 0.875 0.826 0.382 0.164 0.022 0.835 0.946
7  0.301 0.892 0.855 0.638 0.580 0.179 0.042 0.781 0.932
8  0.324 0.985 0.725 0.538 0.649 0.018 0.118 0.968 0.847
```

```
9  0.329 0.940 0.943 0.684 0.589 0.089 0.018 0.885 0.971
10 0.359 0.844 0.750 0.720 0.286 0.238 0.053 0.751 0.843
11 0.390 0.869 0.739 0.550 0.630 0.130 0.142 0.809 0.816
12 0.415 0.750 1.000 0.982 0.256 0.462 0.000 0.680 1.000
13 0.438 0.909 0.727 0.463 0.571 0.060 0.167 0.886 0.774
14 0.477 0.887 0.957 0.580 0.608 0.081 0.025 0.877 0.961
15 0.492 0.833 0.934 0.556 0.655 0.115 0.044 0.829 0.936
16 0.529 0.800 1.000 0.878 0.522 0.196 0.000 0.818 1.000
17 0.537 0.743 1.000 0.839 0.361 0.250 0.000 0.770 1.000
18 0.552 1.000 0.789 0.308 0.938 0.000 0.308 1.000 0.753
19 0.608 0.792 0.933 0.613 0.583 0.104 0.065 0.855 0.900
20 0.626 0.847 0.917 0.686 0.750 0.074 0.114 0.903 0.868
21 0.654 0.930 0.958 0.615 0.748 0.024 0.062 0.962 0.924
22 0.707 0.808 1.000 0.778 0.631 0.077 0.000 0.910 1.000
23 0.744 0.756 0.971 0.775 0.586 0.086 0.050 0.900 0.921
24 0.750 0.769 0.981 0.606 0.515 0.061 0.030 0.909 0.944
25 0.767 0.547 0.984 0.854 0.459 0.215 0.024 0.799 0.950
26 0.782 1.000 0.968 0.735 0.738 0.000 0.088 1.000 0.893
27 0.838 0.595 0.982 0.909 0.581 0.120 0.055 0.884 0.914
28 0.852 0.611 1.000 0.880 0.729 0.097 0.000 0.901 1.000
29 0.864 0.316 0.984 0.333 0.535 0.114 0.056 0.745 0.906
30 0.884 0.400 1.000 0.800 0.395 0.158 0.000 0.835 1.000
```

In this case, it is possible to obtain the same values for $Sp = TNR$ using a single threshold: quality.threshold(ref, -test, -25)$indices['Sp'] and for $Se = TPR$ using quality.threshold(ref, -test, -21)$indices['Se'].

The correlations between the predictive values and prevalence are reduced but still considerable:

```
R> round(cor(indm2[,'prev'],
R+           indm2[,c('NPV', 'PPV', 'TNR', 'TPR', 'SNPV', 'SPPV')]), 2)

       NPV  PPV  TNR  TPR SNPV SPPV
[1,] -0.72 0.59 0.16 0.04 0.08  0.2
```

However, there is an increase in the number of centers with sufficient classification accuracy:

```
R> which(indm2[,'NPV'] >= .8)

 1  2  3  4  5  6  7  8  9 10 11 13 14 15 16 18 20 21 22 26
 1  2  3  4  5  6  7  8  9 10 11 13 14 15 16 18 20 21 22 26

R> which(indm2[,'PPV'] >= .8)

 1  3  4  5  6  7  9 12 14 15 16 17 19 20 21 22 23 24 25 26 27 28 29 30
 1  3  4  5  6  7  9 12 14 15 16 17 19 20 21 22 23 24 25 26 27 28 29 30
```

```
R> which(indm2[,'PPV'] >= .8 & indm2[,'NPV'] >= .8)

 1  3  4  5  6  7  9 14 15 16 20 21 22 26
 1  3  4  5  6  7  9 14 15 16 20 21 22 26
```

There are now 20 centers with $NPV >= .8$ and 24 centers with $PPV >= .8$. For both PPV and NPV, 14 centers can use the MoCA in this manner to classify both patients with and without CI correctly in at least 4 out of 5 cases.

The results for $TNR = Sp$ and $TPR = Se$ are lower compared to the table based on the optimal dichotomization. The indices $TNR = Sp, TPR = Se, FNR$ and FPR are single cut-point indices. The application of the single cut-point indices Se and Sp is problematic in the context of trichotomization and underestimate the percentages of patients without and with the targeted disease that are identified correctly. The reason for this is that all test scores in the uncertain interval are treated as errors in stead of more cautious classifications. When these test scores are considered as uncertain, another possible line of action can be chosen. A more cautious line of action reduces over-treatment and treatment errors.

The indices Se and Sp are meant for a dichotomous classification and are cumbersome to apply when using a three-way classification. A possible alternative is ignoring the uncertain test scores (function `quality.uncertain`) for the calculation of the test indices.

7. Alternative software

Trichotomization software is scarce. The earlier developed software for the Two-Graphs receiver Operating Characteristics (Greiner 1995, 1996) is no longer available. A non-parametric implementation of function `TGROC` is available in package (**DiagnosisMed**, which is under development (Brasil 2018). For the Grey zone method (Coste *et al.* 2006; Coste and Pouchot 2003) software is not available. Both a `TG-ROC` and a `greyzone` function have been made part of the **UncertainInterval** package.
I also like to point to an alternative R package for trichotomization: **ThreshholdROC** (Perez-Jaume, Skaltsa, Pallarès, and Carrasco 2017). This method is most suitable when there are three distinguishable underlying states and is especially suitable for tests that allow for a finer distinction. When underlying states are less easy to distinguish in three different states, a middle range of test scores is better considered as uncertain and the package **UncertainInterval** may be a better choice.

8. Discussion

The **UncertainInterval** package allows for the identification of a middle range of uncertain test scores. The main advantage is that it enables identification of test scores that have about equal likelihood of identifying a patient with or without the targeted impairment. The application on the MoCA shows that a large number of classification errors are prevented when considering these test scores as uncertain. Choosing a more cautious line of action such as awaiting further developments while applying active surveillance or watchful waiting is considered best practice for a disease such as prostate cancer (Bangma *et al.* 2013). Knowing which range of test scores are inconclusive concerning the targeted disease may help in considering benefits and costs

both for patients with and without the targeted disease.
This paper also shows a secondary benefit of considering a range of test scores as uncertain: it allows the application of trichotomized cutoff scores that can be applied in a wider range of clinical settings as they offer sufficient classification accuracy in more settings that vary in the mix of patients with and without the targeted disease. While this does not solve the problem of prevalence, it does alleviate it.

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