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Asymptotic Properties of the Sequential Empirical ROC and PPV Curves

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Abstract

The receiver operating characteristic (ROC) curve, the positive predictive value (PPV) curve and the negative predictive value (NPV) curve are three common measures of performance for a diagnostic biomarker. The independent increments covariance structure assumption is common in the group sequential study design literature. Showing that summary measures of the ROC, PPV and NPV curves have an independent increments covariance structure will provide the theoretical foundation for designing group sequential diagnostic biomarker studies. The ROC, PPV and NPV curves are often estimated empirically to avoid assumptions about the distributional form of the biomarkers. In this paper we derive asymptotic theory for the sequential empirical ROC, PPV and NPV curves. These results are used to show that the independent increments assumption holds for some summary measures of the ROC, PPV and NPV curves when estimated empirically.

1 Introduction

Diagnostic biomarkers are used to classify a patient as a case or a control. Two common approaches for evaluating a diagnostic biomarker are to summarize the markers classification and predictive accuracy. Classification accuracy refers to the biomarker's ability to, conditional on the subjects true case/control status, correctly classify the subject as a case or control. Predictive accuracy refers to the biomarker's ability to, conditional on the biomarker value, predict if a subject is truly a case or control.

A dichotomous biomarker can only take the values positive or negative and therefore it is straightforward to summarize its classification and predictive accuracy. In contrast, a threshold must be defined in order to translate a continuous biomarker into a positive or negative test result. In the setting of case-control sampling, where disease status is known before sampling, let X_D be a biomarker value for a case with cumulative distribution function $F_D(x)$ and $X_{\bar{D}}$ be a biomarker value for a control with cumulative distribution function $F_{\bar{D}}(x)$. In the setting of cohort sampling, where disease status is unknown before sampling from a well defined cohort, let D be a Bernoulli random variable indicating disease status with prevalence ρ and let X be a biomarker value with conditional distribution $F(x|D=1) = F_D(x)$ and $F(x|D=0) = F_{\bar{D}}(x)$. The marginal distribution of X is therefore $F(x) = \rho F_D(x) + (1-\rho)\, F_{\bar{D}}(x)$. In both cases, we assume that larger biomarker values are more indicative of disease. Therefore, for a threshold c, a biomarker value X_D, $X_{\bar{D}}$ or X is translated into a positive test result if it is greater than c and a negative test result if it is less than or equal to c.

The receiver operating characteristic (ROC) curve summarizes the classification accuracy of a continuous marker (Pepe, 2003). The classification accuracy of a dichotomous biomarker is summarized by the sensitivity and specificity. This can be extended to continuous markers by defining a threshold and reporting the sensitivity and specificity of the dichotomous marker derived from this threshold. For a given threshold c, the classification accuracy of the biomarker can be summarized by the true positive fraction (TPF), $TPF(c) = P\,[X > c|D = 1] = P[X_D > c]$, and the false positive fraction (FPF), $FPF(c) = P\,[X > c|D = 0] = P[X_{\bar{D}} > c]$. The entire set of possible true and false positive fractions can be summarized by the (ROC) curve

$$ROC(c) = \{(TPF(c), FPF(c)), c \in (-\infty, \infty)\}.$$

The ROC curve can alternately be expressed as

$$ROC(t) = S_D\left(S_{\bar{D}}^{-1}(t)\right), \ t \in (0,1), \tag{1}$$

where $S_D(x) = 1 - F_D(x)$ and $S_{\bar{D}}(x) = 1 - F_{\bar{D}}(x)$. $ROC(t)$ can be interpreted as the TPF corresponding to a FPF of t. Alternately, one might be interested in the inverse of the ROC curve,

$$ROC^{-1}(v) = S_{\bar{D}}\left(S_D^{-1}(v)\right), \ v \in (0,1). \tag{2}$$

$ROC^{-1}(v)$ is indexed by the TPF and can be interpreted as the FPF corresponding to a TPF of v.

The predictive accuracy of a dichotomous biomarker can be summarized by the positive predictive value (PPV) and negative predictive value (NPV). The PPV and NPV curves were proposed as an extension of PPV and NPV to continuous markers (Moskowitz and Pepe, 2004; Zheng et al., 2008). For a given threshold c, the predictive accuracy of the biomarker can be summarized by the positive predictive value, $PPV(c) = P[D = 1|X > c]$, and the negative predictive value, $NPV(c) = P[D = 0|X \leq c]$. The PPV and NPV curves are defined as $PPV(c)$ and $NPV(c)$ for all $c \in (-\infty, \infty)$. In practice, the PPV and NPV curves are indexed by a summary of the marker distribution rather than a generic threshold. In this paper, we consider the PPV and NPV curves indexed by the TPF, FPF and the percentile value in the entire population.

The ROC, PPV and NPV curves are commonly estimated nonparametrically using the empirical ROC curve, the empirical PPV curve and the empirical NPV curve, respectively. Nonparametric estimation allows us to avoid making assumptions about the form of $F_D(x)$ and $F_{\bar{D}}(x)$. This is particularly important in the case of the ROC, PPV and NPV curves because our interest often lies in regions of the curve that correspond to the tails of the distributions. For example, a biomarker must possess a high specificity in order to be clinically useful in a low disease risk population screening setting, which corresponds to the upper tail of the distribution of the biomarker in the controls.

Our understanding of the empirical ROC curve is enhanced by knowledge of it's asymptotic properties. Hsieh and Turnbull (1996) showed that the empirical ROC curve converges to the sum of two independent Brownian bridges. The asymptotic normality of summary measures of the empirical ROC curve, such as the area under the ROC curve or a point on the ROC curve, can be derived as a result of their work. Currently, no asymptotic theory is available for the empirical PPV and NPV curves.

Group sequential study designs provide an opportunity to improve the efficiency of diagnostic biomarker studies. Many group sequential methods assume an independent increments covariance structure (Jennison and Turnbull, 2000). These methods could be applied to any summary of the ROC, PPV or NPV curve for which this assumption holds. Tang et al. (2008) recently showed that a family of weighted area under the ROC curve (wAUC) statistics has an independent increments covariance structure and illustrate how this family of statistics can be used to design group sequential diagnostic biomarker studies. Showing that a wide array of summaries of the ROC, PPV and NPV curves have an independent increment covariance structure will allow more flexibility when designing group sequential diagnostic biomarker studies.

In this paper we investigate the asymptotic properties of the sequential empirical ROC, PPV and NPV curves. We first define the sequential empirical estimates of the underlying distribution and quantile functions under case-control and cohort sampling. Under case-control sampling, let $X_{D,1}, X_{D,2}, \ldots, X_{D,n_D}$ be the marker values for the cases with distribution function, $F_D(x)$, and $X_{\bar{D},1}, X_{\bar{D},2}, \ldots, X_{\bar{D},n_{\bar{D}}}$ be the marker values for the controls with distribution function, $F_{\bar{D}}(x)$. Furthermore, we let r_D and $r_{\bar{D}}$ refer to the proportion of case and controls, respectively, that are observed at a given time point. The sequential empirical estimate of $F_D(x)$ is defined as

$$\hat{F}_{D,r_D}(x) = \begin{cases} 0, & 0 \leq r_D < \frac{1}{n_D}, \\ \frac{1}{[r_D n_D]} \sum_{i=1}^{[r_D n_D]} 1\{X_{D,i} \leq x\}, & -\infty < x < \infty, \quad \frac{1}{n_D} \leq r_D \leq 1, \end{cases}$$

and the sequential empirical estimate of $F_D^{-1}(t)$ is defined as

$$\hat{F}^{-1}_{D,r_D}(t) = \begin{cases} X_{D,1,[r_D n_D]} & if \quad t = 0, \quad 0 \leq r_D \leq 1, \\ X_{D,k,[r_D n_D]} & if \quad \frac{k-1}{[r_D n_D]} < t \leq \frac{k}{[r_D n_D]}, \\ & 1 \leq k \leq [r_D n_D], 0 \leq t \leq 1 \end{cases}$$

where $X_{D,1,[r_D n_D]}, X_{D,2,[r_D n_D]}, \ldots, X_{D,[r_D n_D],[r_D n_D]}$ are the sequential order statistics of the biomarker values for the cases. The sequential empirical estimates of $S_D(x)$ and $S_D^{-1}(t)$ are defined as $\hat{S}_{D,r_D}(x) = 1 - \hat{F}_{D,r_D}(x)$ and $\hat{S}^{-1}_{D,r_D}(t) = \hat{F}^{-1}_{D,r_D}(1-t)$. The sequential empirical estimates for the control population are defined analagously. The sequential empirical estimates of $F_D(x)$ and $F_{\bar{D}}(x)$ lead to a natural definition of the sequential empirical estimates of $F(x)$ and $F^{-1}(t)$ under case-control sampling,

$$\hat{F}_{r_D, r_{\bar{D}}}(x) = \rho \hat{F}_{D,r_D}(x) + (1-\rho)\,\hat{F}_{\bar{D},r_{\bar{D}}}(x)$$

and

$$\hat{F}^{-1}_{r_D, r_{\bar{D}}}(t) = \inf\{x : \hat{F}_{r_D, r_{\bar{D}}}(x) \geq t\},$$

where ρ is assumed to be known.

Under cohort sampling, let $D_1, D_2, \ldots, D_n$ be i.i.d. Bernoulli random variables indicating disease status with prevalence ρ, let $X_1, X_2, \ldots, X_n$ be biomarker values with conditional distribution $F(x|D=1) = F_D(x)$ and $F(x|D=0) = F_{\bar{D}}(x)$ and let r refer to the proportion of subjects observed at a given time point. The marginal distribution of the $X_i's$ is $F(x) = \rho F_D(x) + (1-\rho)\,F_{\bar{D}}(x)$. The sequential empirical estimate of $F_D(x)$ under cohort sampling is defined as

$$\hat{F}_{D,r}(x) = \begin{cases} 0, & 0 \leq r < \frac{1}{n}, \\ \frac{\hat{P}_r(X \leq x, D=1)}{\hat{\rho}_r}, & -\infty < x < \infty, \quad \frac{1}{n} \leq r \leq 1, \end{cases}$$

where

$$\hat{P}_r(X \leq x, D=1) = \begin{cases} 0, & 0 \leq r < \frac{1}{n}, \\ \frac{1}{[rn]} \sum_{i=1}^{[rn]} 1\{X_i \leq x, D_i = 1\}, \quad -\infty < x < \infty, & \frac{1}{n} \leq r \leq 1, \end{cases}$$

and

$$\hat{\rho}_r = \frac{1}{[rn]} \sum_{i=1}^{[rn]} D_i.$$

The sequential empirical estimate of $F_D^{-1}(t)$ under cohort sampling is defined as

$$\hat{F}_{D,r}^{-1}(t) = \inf\{x : \hat{F}_{D,r}(x) \geq t\}.$$

Again, the sequential empirical estimates of $S_D(x)$ and $S_D^{-1}(t)$ are defined as $\hat{S}_{D,r}(x) = 1 - \hat{F}_D(x)$ and $\hat{S}_{D,r}^{-1}(t) = \hat{F}_{D,r}^{-1}(1-t)$ and the sequential empirical estimates for the control population are defined analagously. The sequential empirical estimate of $F(x)$ is

$$\hat{F}_r(x) = \begin{cases} 0, & 0 \leq r < \frac{1}{n}, \\ \frac{1}{[rn]} \sum_{i=1}^{[rn]} 1\{X_i \leq x\}, \quad -\infty < x < \infty, & \frac{1}{n} \leq r \leq 1, \end{cases}$$

and the sequential empirical estimate of $F^{-1}(t)$ is

$$\hat{F}_r^{-1}(t) = \begin{cases} X_{1,[rn]} & if \quad t = 0, \quad 0 \leq r \leq 1, \\ X_{k,[rn]} & if \quad \frac{k-1}{[rn]} < t \leq \frac{k}{[rn]}, \\ & 1 \leq k \leq [rn], 0 \leq t \leq 1, \end{cases}$$

where $X_{1,[rn]}, X_{2,[rn]}, \ldots, X_{[rn],[rn]}$ are the sequential order statistics of the biomarker values in the entire population.

Throughout this paper we let $0 < a < b < 1$, $0 < c < 1$, $0 < d < 1$, $0 < e < 1$ and make the following assumptions:

A1 $F_D(x)$ and $F_{\bar{D}}(x)$ are continuous distribution functions with continuous densities $f_D(x)$ and $f_{\bar{D}}(x)$, respectively,

A2 $f_D(x) > 0$ for $x \in (\sup\{x : F_D(x) = 0\}, \inf\{x : F_D(x) = 1\})$,

A3 $f_{\bar{D}}(x) > 0$ for $x \in (\sup\{x : F_{\bar{D}}(x) = 0\}, \inf\{x : F_{\bar{D}}(x) = 1\})$,

and under case-control sampling we also assume

A4 $\frac{n_D}{n_{\bar{D}}} \to \lambda > 0$ as $n_D \to \infty$ and $n_{\bar{D}} \to \infty$.

In section 2 we extend the work of Hsieh and Turnbull (1996) to the sequential empirical ROC curve and use this result to show that the sequential empirical estimate of $ROC(t)$, a point on the ROC curve, has an independent increments covariance structure. In Sections 3, 4 and 5 we consider the PPV and NPV curves indexed by the true positive fraction, false positive fraction and the percentile value in the entire population, respectively. Distribution theory is developed for the sequential empirical PPV and NPV curves along with some of their summary measures. Distribution theory for the fixed-sample empirical PPV and NPV curves is developed as a special case.

2 ROC curve

2.1 Under Case-Control Sampling

We first consider the sequential empirical estimate of the ROC curve. In most instances the ROC curve is estimated from case-control sampling and therefore we assume case-control sampling at this point. The sequential empirical estimate of the ROC curve, $\widehat{ROC}_{r_D, r_D}(t)$, is defined by substituting the sequential empirical estimates of $S_D(x)$ and $S_{\bar{D}}(x)$ into (1)

$$\widehat{ROC}_{r_D, r_{\bar{D}}}(t) = \hat{S}_{D, r_D}\left(\hat{S}^{-1}_{\bar{D}, r_{\bar{D}}}(t)\right).$$

The sequential empirical estimate of $ROC^{-1}(v)$ is defined similarly. Theorem 2.1 establishes the convergence in distribution of the sequential empirical ROC curve and the inverse of the ROC curve to the sum of two independent Kiefer processes.

Theorem 2.1. *Assume A1-A4 hold.*

A. *Let* $\frac{f_D(S_{\bar{D}}^{-1}(t))}{f_{\bar{D}}(S_{\bar{D}}^{-1}(t))}$ *be bounded on* $[a,b]$. *As* $n_D \to \infty$ *and* $n_{\bar{D}} \to \infty$

$$n_D^{-1/2}[n_D r_D](\widehat{ROC}_{r_D, r_{\bar{D}}}(t) - ROC(t)) \to_D K_1(ROC(t), r_D) + \lambda^{1/2} \frac{r_D}{r_{\bar{D}}} \left(\frac{f_D(S_{\bar{D}}^{-1}(t))}{f_{\bar{D}}(S_{\bar{D}}^{-1}(t))} \right) K_2(t, r_{\bar{D}})$$

uniformly for $t \in [a,b]$, $r_D \in [c,1]$ *and* $r_{\bar{D}} \in [d,1]$ *where* K_1 *and* K_2 *are independent Kiefer Processes.*

B. *Let* $\frac{f_{\bar{D}}(S_D^{-1}(v))}{f_D(S_D^{-1}(v))}$ *be bounded on* $[a,b]$. *As* $n_D \to \infty$ *and* $n_{\bar{D}} \to \infty$

$$n_D^{-1/2}[n_D r_D](\widehat{ROC}^{-1}_{r_D, r_{\bar{D}}}(v) - ROC^{-1}(v)) \to_D \lambda^{-1/2} \frac{r_D}{r_{\bar{D}}} K_2(ROC^{-1}(v), r_{\bar{D}}) + \left(\frac{f_{\bar{D}}(S_D^{-1}(v))}{f_D(S_D^{-1}(v))} \right) K_1(v, r_D)$$

uniformly for $v \in [a,b]$, $r_D \in [c,1]$ *and* $r_{\bar{D}} \in [d,1]$ *where* K_1 *and* K_2 *are independent Kiefer Processes.*

Proof. We present the proof of A and note that the proof of B is nearly identical. First, note that

$$\begin{aligned} n_D^{-1/2}[n_D r_D](R\hat{O}C_{r_D, r_{\bar{D}}}(t) - ROC(t)) =& n_D^{-1/2}[n_D r_D] \left(\hat{S}_{D, r_D}(\hat{S}^{-1}_{\bar{D}, r_{\bar{D}}}(t)) - S_D(S_{\bar{D}}^{-1}(t)) \right) \\ =& n_D^{-1/2}[n_D r_D] \left(\hat{S}_{D, r_D}(\hat{S}^{-1}_{\bar{D}, r_{\bar{D}}}(t)) - S_D(\hat{S}^{-1}_{\bar{D}, r_{\bar{D}}}(t)) \right) \\ &+ n_D^{-1/2}[n_D r_D] \left(S_D(\hat{S}^{-1}_{\bar{D}, r_{\bar{D}}}(t)) - S_D(S_{\bar{D}}^{-1}(t)) \right). \end{aligned}$$

The first term converges to a Kiefer process. We note that

$$\begin{aligned} \sup_{c \le r_D \le 1} \sup_{d \le r_{\bar{D}} \le 1} \sup_{a \le t \le b} \left| F_{\bar{D}} \left(\hat{F}^{-1}_{\bar{D}, r_{\bar{D}}}(t) \right) - t \right| =& \frac{n_{\bar{D}}}{[n_{\bar{D}} d]} \sup_{c \le r_D \le 1} \sup_{d \le r_{\bar{D}} \le 1} \sup_{a \le t \le b} \frac{[n_{\bar{D}} d]}{n_{\bar{D}}} \left| F_{\bar{D}} \left(\hat{F}^{-1}_{\bar{D}, r_{\bar{D}}}(t) \right) - t \right| \\ \le& \frac{n_{\bar{D}}}{[n_{\bar{D}} d]} \sup_{c \le r_D \le 1} \sup_{d \le r_{\bar{D}} \le 1} \sup_{a \le t \le b} \frac{[n_{\bar{D}} r_{\bar{D}}]}{n_{\bar{D}}} \left| F_{\bar{D}} \left(\hat{F}^{-1}_{\bar{D}, r_{\bar{D}}}(t) \right) - t \right|. \end{aligned}$$

Therefore

$$\sup_{c \le r_D \le 1} \sup_{d \le r_{\bar{D}} \le 1} \sup_{a \le t \le b} \left| F_{\bar{D}} \left(\hat{F}^{-1}_{\bar{D}, r_{\bar{D}}}(t) \right) - t \right| \to_{a.s.} 0 \tag{3}$$

by the Glivenko-Cantelli Theorems (1.51 and 1.52 in Csörgő and Szyszkowicz (1998)) and because $\frac{n_{\bar{D}}}{[n_{\bar{D}} d]} \to \frac{1}{d}$.

Furthermore, $F_{\bar{D}}^{-1}(t)$ will be continuous by A1-A3 and will be uniformly continuous on $[a, b]$. Therefore,

$$\sup_{c\le r_D\le 1}\sup_{d\le r_{\bar{D}}\le 1}\sup_{a\le t\le b}\left|\hat{F}_{\bar{D},r_{\bar{D}}}^{-1}(t) - F_{\bar{D}}^{-1}(t)\right| \rightarrow_{a.s.} 0. \tag{4}$$

We note that due to the continuity of $F_{\bar{D}}(x)$, $S_{\bar{D}}^{-1}(t) = F_{\bar{D}}^{-1}(1-t)$ and therefore (4) also applies to $S_{\bar{D}}^{-1}(t)$. From corollary 1.A in Csörgő and Szyszkowicz (1998), (4) and the uniform continuity of the Kiefer process, we have

$$n_D^{-1/2}[n_D r_D]\left(\hat{S}_{D,r_D}(\hat{S}_{\bar{D},r_{\bar{D}}}^{-1}(t)) - S_D(\hat{S}_{\bar{D},r_{\bar{D}}}^{-1}(t))\right) \rightarrow_D K_1(ROC(t), r_D). \tag{5}$$

The second term can be re-written as

$$\begin{aligned}
&n_D^{-1/2}[n_D r_D]\left(S_D(\hat{S}_{\bar{D},r_{\bar{D}}}^{-1}(t)) - S_D(S_{\bar{D}}^{-1}(t))\right)\\
=&n_D^{-1/2}[n_D r_D]\left(S_D\left(S_{\bar{D}}^{-1}\left(S_{\bar{D}}\left(\hat{S}_{\bar{D},r_{\bar{D}}}^{-1}(t)\right)\right)\right) - S_D\left(S_{\bar{D}}^{-1}(t)\right)\right)\\
=&\frac{n_D^{-1/2}[n_D r_D]}{n_{\bar{D}}^{-1/2}[n_{\bar{D}} r_{\bar{D}}]}\frac{\left(S_D\left(S_{\bar{D}}^{-1}\left(S_{\bar{D}}\left(\hat{S}_{\bar{D},r_{\bar{D}}}^{-1}(t)\right)\right)\right) - S_D\left(S_{\bar{D}}^{-1}(t)\right)\right)}{S_{\bar{D}}\left(\hat{S}_{\bar{D},r_{\bar{D}}}^{-1}(t)\right) - t}n_{\bar{D}}^{-1/2}[n_{\bar{D}} r_{\bar{D}}]\left(S_{\bar{D}}\left(\hat{S}_{\bar{D},r_{\bar{D}}}^{-1}(t)\right) - t\right)\\
=&\frac{n_D^{-1/2}[n_D r_D]}{n_{\bar{D}}^{-1/2}[n_{\bar{D}} r_{\bar{D}}]}\frac{\left(S_D\left(S_{\bar{D}}^{-1}\left(S_{\bar{D}}\left(\hat{S}_{\bar{D},r_{\bar{D}}}^{-1}(t)\right)\right)\right) - S_D\left(S_{\bar{D}}^{-1}(t)\right)\right)}{S_{\bar{D}}\left(\hat{S}_{\bar{D},r_{\bar{D}}}^{-1}(t)\right) - t}n_{\bar{D}}^{-1/2}[n_{\bar{D}} r_{\bar{D}}]\left(S_{\bar{D}}\left(\hat{S}_{\bar{D},r_{\bar{D}}}^{-1}(t)\right) - \hat{S}_{\bar{D},r_{\bar{D}}}\left(\hat{S}_{\bar{D},r_{\bar{D}}}^{-1}(t)\right)\right)\\
&+\frac{n_D^{-1/2}[n_D r_D]}{n_{\bar{D}}^{-1/2}[n_{\bar{D}} r_{\bar{D}}]}\frac{\left(S_D\left(S_{\bar{D}}^{-1}\left(S_{\bar{D}}\left(\hat{S}_{\bar{D},r_{\bar{D}}}^{-1}(t)\right)\right)\right) - S_D\left(S_{\bar{D}}^{-1}(t)\right)\right)}{S_{\bar{D}}\left(\hat{S}_{\bar{D},r_{\bar{D}}}^{-1}(t)\right) - t}n_{\bar{D}}^{-1/2}[n_{\bar{D}} r_{\bar{D}}]\left(\hat{S}_{\bar{D},r_{\bar{D}}}\left(\hat{S}_{\bar{D},r_{\bar{D}}}^{-1}(t)\right) - t\right).
\end{aligned}$$

By the mean value theorem, there exists a $S_{\bar{D}}\left(\tilde{S}_{\bar{D},r_{\bar{D}}}^{-1}(t)\right)$ between $S_{\bar{D}}\left(\hat{S}_{\bar{D},r_{\bar{D}}}^{-1}(t)\right)$ and t such that

$$\frac{S_D\left(S_{\bar{D}}^{-1}\left(S_{\bar{D}}\left(\hat{S}_{\bar{D},r_{\bar{D}}}^{-1}(t)\right)\right)\right) - S_D\left(S_{\bar{D}}^{-1}(t)\right)}{S_{\bar{D}}\left(\hat{S}_{\bar{D},r_{\bar{D}}}^{-1}(t)\right) - t} = \frac{f_D\left(S_{\bar{D}}^{-1}\left(S_{\bar{D}}\left(\tilde{S}_{\bar{D},r_{\bar{D}}}^{-1}(t)\right)\right)\right)}{f_{\bar{D}}\left(S_{\bar{D}}^{-1}\left(S_{\bar{D}}\left(\tilde{S}_{\bar{D},r_{\bar{D}}}^{-1}(t)\right)\right)\right)}.$$

From (3), we know that $S_{\bar{D}}\left(\hat{S}_{\bar{D},r_{\bar{D}}}^{-1}(t)\right) \rightarrow_{a.s.} t$, uniformly for $t \in [a, b]$, $r_D \in [c, 1]$ and $r_{\bar{D}} \in [d, 1]$, and, therefore, $S_{\bar{D}}\left(\tilde{S}_{\bar{D},r_{\bar{D}}}^{-1}(t)\right) \rightarrow_{a.s.} t$, uniformly for $t \in [a, b]$, $r_D \in [c, 1]$ and $r_{\bar{D}} \in [d, 1]$. This, along with the uniform continuity of $\frac{f_D(S_{\bar{D}}^{-1}(t))}{f_{\bar{D}}(S_{\bar{D}}^{-1}(t))}$, allows us to conclude that

$$\sup_{c\le r_D\le 1}\sup_{d\le r_{\bar{D}}\le 1}\sup_{a\le t\le b}\left|\frac{f_D\left(S_{\bar{D}}^{-1}\left(S_{\bar{D}}\left(\tilde{S}_{\bar{D},r_{\bar{D}}}^{-1}(t)\right)\right)\right)}{f_{\bar{D}}\left(S_{\bar{D}}^{-1}\left(S_{\bar{D}}\left(\tilde{S}_{\bar{D},r_{\bar{D}}}^{-1}(t)\right)\right)\right)} - \frac{f_D\left(S_{\bar{D}}^{-1}(t)\right)}{f_{\bar{D}}\left(S_{\bar{D}}^{-1}(t)\right)}\right| \rightarrow_{a.s.} 0,$$

which implies,

$$\sup_{c\le r_D\le 1}\sup_{d\le r_{\bar{D}}\le 1}\sup_{a\le t\le b}\left|\frac{S_D\left(S_{\bar{D}}^{-1}\left(S_{\bar{D}}\left(\hat{S}_{\bar{D},r_{\bar{D}}}^{-1}(t)\right)\right)\right)-S_D\left(S_{\bar{D}}^{-1}(t)\right)}{S_{\bar{D}}\left(\hat{S}_{\bar{D},r_{\bar{D}}}^{-1}(t)\right)-t}-\frac{f_D\left(S_{\bar{D}}^{-1}(t)\right)}{f_{\bar{D}}\left(S_{\bar{D}}^{-1}(t)\right)}\right|\to_{a.s.} 0. \tag{6}$$

For all $r_{\bar{D}}\in[d,1]$,

$$\sup_{a\le t\le b}\left|\hat{S}_{\bar{D},r_{\bar{D}}}\left(\hat{S}_{\bar{D},r_{\bar{D}}}^{-1}(t)\right)-t\right|\le_{a.s.}\frac{1}{[n_{\bar{D}}r_{\bar{D}}]}.$$

Therefore,

$$\sup_{c\le r_D\le 1}\sup_{d\le r_{\bar{D}}\le 1}\sup_{a\le t\le b} n_{\bar{D}}^{-1/2}[n_{\bar{D}}r_{\bar{D}}]\left|\hat{S}_{\bar{D},r_{\bar{D}}}\left(\hat{S}_{\bar{D},r_{\bar{D}}}^{-1}(t)\right)-t\right|\le_{a.s.}\frac{1}{n_{\bar{D}}^{1/2}},$$

and

$$\sup_{c\le r_D\le 1}\sup_{d\le r_{\bar{D}}\le 1}\sup_{a\le t\le b} n_{\bar{D}}^{-1/2}[n_{\bar{D}}r_{\bar{D}}]\left|\hat{S}_{\bar{D},r_{\bar{D}}}\left(\hat{S}_{\bar{D},r_{\bar{D}}}^{-1}(t)\right)-t\right|\to_{a.s.} 0. \tag{7}$$

From corollary 1.A in Csörgő and Szyszkowicz (1998), (4) and the uniform continuity of the Kiefer process, we have

$$n_{\bar{D}}^{-1/2}[n_{\bar{D}}r_{\bar{D}}]\left(S_{\bar{D}}\left(\hat{S}_{\bar{D},r_{\bar{D}}}^{-1}(t)\right)-\hat{S}_{\bar{D},r_{\bar{D}}}\left(\hat{S}_{\bar{D},r_{\bar{D}}}^{-1}(t)\right)\right)\to_D K_2(t,r_{\bar{D}}). \tag{8}$$

By (6), (7), (8) and noting that $\frac{n_D^{-1/2}[n_D r_D]}{n_{\bar{D}}^{-1/2}[n_{\bar{D}}r_{\bar{D}}]}\to\lambda^{1/2}\frac{r_D}{r_{\bar{D}}}$, we conclude that

$$n_D^{-1/2}[n_D r_D]\left(S_D(\hat{S}_{\bar{D},r_{\bar{D}}}^{-1}(t))-S_D(S_{\bar{D}}^{-1}(t))\right)\to_D\lambda^{1/2}\frac{r_D}{r_{\bar{D}}}\left(\frac{f_D(S_{\bar{D}}^{-1}(t))}{f_{\bar{D}}(S_{\bar{D}}^{-1}(t))}\right)K_2(t,r_{\bar{D}}). \tag{9}$$

Summing (5) and (9) gives the desired result. □

Theorem 2.1 extends the work of Hsieh and Turnbull to the sequential empirical ROC curve. We see that the result is nearly identical to Hsieh and Turnbull's result with Kiefer Processes replacing Brownian Bridges. In fact, we are able to recover Hsieh and Turnbull's result as a corollary.

Corollary 2.2. *Assume A1-A4 hold.*

A. Let $\frac{f_D(S_{\bar{D}}^{-1}(t))}{f_{\bar{D}}(S_{\bar{D}}^{-1}(t))}$ *be bounded on* $[a,b]$*. As* $n_D\to\infty$ *and* $n_{\bar{D}}\to\infty$

$$n_D^{1/2}(\widehat{ROC}_{1,1}(t)-ROC(t))\to_D B_1(ROC(t))+\lambda^{1/2}\left(\frac{f_D(S_{\bar{D}}^{-1}(t))}{f_{\bar{D}}(S_{\bar{D}}^{-1}(t))}\right)B_2(t)$$

uniformly for $t \in [a,b]$ where B_1 and B_2 are independent Brownian Bridges.

B. *Let $\frac{f_{\bar{D}}(S_D^{-1}(v))}{f_D(S_D^{-1}(v))}$ be bounded on $[a,b]$. As $n_D \to \infty$ and $n_{\bar{D}} \to \infty$*

$$n_D^{1/2}(\widehat{ROC}_{1,1}^{-1}(v) - ROC^{-1}(v)) \to_D \lambda^{-1/2} B_2(ROC^{-1}(v)) + \left(\frac{f_{\bar{D}}(S_D^{-1}(v))}{f_D(S_D^{-1}(v))}\right) B_1(v)$$

uniformly for $v \in [a,b]$ where B_1 and B_2 are independent Brownian Bridges.

Proof. Immediate from Theorem 2.1 and by noting that $K(t,1) =_D B(t)$. □

Our ability to implement group sequential methodology for diagnostic biomarker studies will be enhanced by showing that summary measures of the ROC curve have an independent increments covariance structure when estimated sequentially. From Theorem 2.1 we are able to derive distribution theory for the sequential empirical estimates of summary measures of the *ROC* curve. Corollary 2.3 shows that the sequential empirical estimate of $ROC(t)$, a point on the ROC curve, has an independent increments covariance structure.

Corollary 2.3. *Assume A1-A4 hold.*

A. *Let $\frac{f_D(S_{\bar{D}}^{-1}(t))}{f_{\bar{D}}(S_{\bar{D}}^{-1}(t))}$ be bounded on $[a,b]$. For $t \in (0,1)$ and J stopping times, $\left(\widehat{ROC}_{r_{D,1},r_{\bar{D},1}}(t), \widehat{ROC}_{r_{D,2},r_{\bar{D},2}}(t), \ldots, \widehat{ROC}_{r_{D,J},r_{\bar{D},J}}(t)\right)$, is approximately multivariate normal with,*

$$\widehat{ROC}_{r_{D,i},r_{\bar{D},i}}(t) \sim N\left(ROC(t), \sigma^2_{\widehat{ROC}_{r_{D,i},r_{\bar{D},i}}(t)}\right) \qquad i = 1,2,\ldots,J$$

and

$$Cov\left[\widehat{ROC}_{r_{D,i},r_{\bar{D},i}}(t), \widehat{ROC}_{r_{D,j},r_{\bar{D},j}}(t)\right] = Var\left[\widehat{ROC}_{r_{D,j},r_{\bar{D},j}}(t)\right] = \sigma^2_{\widehat{ROC}_{r_{D,j},r_{\bar{D},j}}(t)}, \qquad r_i \le r_j$$

where

$$\sigma^2_{\widehat{ROC}_{r_{D,j},r_{\bar{D},j}}(t)} = \frac{ROC(t)\,(1-ROC(t))}{n_D r_{D,j}} + \left(\frac{f_D(S_{\bar{D}}^{-1}(t))}{f_{\bar{D}}(S_{\bar{D}}^{-1}(t))}\right)^2 \frac{t\,(1-t)}{n_{\bar{D}} r_{\bar{D},j}}.$$

B. *Let $\frac{f_{\bar{D}}(S_D^{-1}(v))}{f_D(S_D^{-1}(v))}$ be bounded on $[a,b]$. For $v \in (0,1)$ and J stopping times,*

$\left(\widehat{ROC}^{-1}_{r_{D,1},r_{\bar{D},1}}(v), \widehat{ROC}^{-1}_{r_{D,2},r_{\bar{D},2}}(v), \ldots, \widehat{ROC}^{-1}_{r_{D,J},r_{\bar{D},J}}(v)\right)$, *is approximately multivariate normal with,*

$$\widehat{ROC}^{-1}_{r_{D,i},r_{\bar{D},i}}(v) \sim N\left(ROC^{-1}(v), \sigma^2_{\widehat{ROC}^{-1}_{r_{D,i},r_{\bar{D},i}}(v)}\right) \qquad i = 1, 2, \ldots, J$$

and

$$Cov\left[\widehat{ROC}^{-1}_{r_{D,i},r_{\bar{D},i}}(v), \widehat{ROC}^{-1}_{r_{D,j},r_{\bar{D},j}}(v)\right] = Var\left[\widehat{ROC}^{-1}_{r_{D,j},r_{\bar{D},j}}(v)\right] = \sigma^2_{\widehat{ROC}^{-1}_{r_{D,j},r_{\bar{D},j}}(v)}, \qquad r_i \leq r_j$$

where

$$\sigma^2_{\widehat{ROC}^{-1}_{r_{D,j},r_{\bar{D},j}}(v)} = \frac{ROC^{-1}(v)\left(1 - ROC^{-1}(v)\right)}{n_{\bar{D}} r_{\bar{D},j}} + \left(\frac{f_{\bar{D}}(S_D^{-1}(v))}{f_D(S_D^{-1}(v))}\right)^2 \frac{v\,(1-v)}{n_D r_{D,j}}.$$

Proof. Immediate from Theorem 2.1. □

2.2 Under Cohort Sampling

We conclude this section by considering the behavior of the sequential empirical estimates of $ROC(t)$ and $ROC(v)^{-1}$ under cohort sampling. These results are not of primary interest because the ROC curve and inverse ROC curve are usually estimated from case-control sampling. We will, though, need these results in the remainder of this chapter. Briefly, the sequential empirical estimates of the ROC curve under cohort sampling is found by substituting the sequential empirical estimates of $S_D(x)$ and $S_{\bar{D}}^{-1}(t)$ under cohort sampling into (1)

$$\widehat{ROC}_r(t) = \hat{S}_{D,r}\left(\hat{S}^{-1}_{\bar{D},r}(t)\right).$$

The sequential empirical estimate of $ROC^{-1}(v)$ is defined in an analagous fashion. We begin by considering the joint asymptotic behavior of $n^{-1/2}[nr]\left(\hat{F}_{D,r}(x) - F_D(x)\right)$, $n^{-1/2}[nr]\left(\hat{F}_{\bar{D},r}(x) - F_{\bar{D}}(x)\right)$ and $n_{-1/2}[nr]\,(\hat{\rho}_r - \rho)$ under cohort sampling.

Lemma 2.4 provides the basis for all remaining asymptotic results that assume cohort sampling.

Lemma 2.4. *Assume A1-A3 hold,*

$$n^{-1/2}[nr]\left(\hat{F}_{D,r}(x)-F_D(x)\right)\to_D \frac{1}{\sqrt{\rho}}K_3\left(F_D(x),r\right),$$

uniformly for $x\in(-\infty,\infty)$ and $r\in[0,1]$,

$$n^{-1/2}[nr]\left(\hat{F}_{\bar{D},r}(x)-F_{\bar{D}}(x)\right)\to_D \frac{1}{\sqrt{1-\rho}}K_4\left(F_{\bar{D}}(x),r\right),$$

uniformly for $x\in(-\infty,\infty)$ and $r\in[0,1]$ and

$$n^{-1/2}[nr]\left(\hat{\rho}_r-\rho\right)\to_D \sqrt{\rho\left(1-\rho\right)}W\left(r\right),$$

uniformly for $r\in[0,1]$, where K_3 and K_4 are independent Kiefer processes and W is a Wiener process that is independent of both K_3 and K_4.

Proof. Let $\mathbb{P}_n=\frac{1}{n}\sum_{i=1}^n\delta_{X_i,D_i}$ be the empirical measure and consider the following class $\mathcal{F}$ of real-valued functions defined on $\mathbb{R}\times\{0,1\}\cup\{\infty\}$:

$$\mathcal{F}=\{1_{[X\le x]}D,1_{[X\le x]}\left(1-D\right):x\in\mathbb{R}\}.$$

Therefore, for $f\in\mathcal{F}$, $\mathbb{P}_nf=\frac{1}{n}\sum_{i=1}^n f\left(X_i,D_i\right)$. $\mathcal{F}$ is a VC class of functions by Lemma 2.6.17 of van der Vaart and Wellner (1996). By combining this with van der Vaart and Wellner (1996), Theorem 2.4.6, page 136 and Theorem 2.5.2, page 127, and noting that $\|f\|_\infty\le 1\equiv F$ for all $f\in\mathcal{F}$, we conclude that $\mathcal{F}$ is $P-$Donsker.. Furthermore, by Theorem 2.12.1 of van der Vaart and Wellner (1996),

$$\frac{1}{\sqrt{n}}\sum_{i=1}^{[nr]}\left(f\left(X_i,D_i\right)-Pf\right)\to_D K\left(f,r\right)$$

in $l^\infty(\mathcal{F}\times[0,1])$ where K is a $P-$Kiefer process. That is, a mean-zero Gaussian process with covariance

$$Cov\left(K\left(f_1,r_1\right),K\left(f_2,r_2\right)\right)=\left(r_1\wedge r_2\right)\left(P\left(f_1f_2\right)-P\left(f_1\right)P\left(f_2\right)\right),$$

for $f_1, f_2 \in \mathcal{F}$ and $r_1, r_2 \in [0,1]$. Therefore,

$$n^{-1/2}[nr]\left(\hat{P}_r\left(X \le x, D=1\right) - P\left(X \le x, D=1\right)\right) \to_D K\left(D1_{[X\le x]}, r\right),$$

$$n^{-1/2}[nr]\left(\hat{P}_r\left(X \le x, D=0\right) - P\left(X \le x, D=0\right)\right) \to_D K\left(\left(1-D\right)1_{[X\le x]}, r\right),$$

and

$$n^{-1/2}[nr]\left(\hat{\rho}_r - \rho\right) \to_D K\left(D, r\right),$$

where K is a $P-$Kiefer process with

$$\begin{aligned} Cov\left(K\left(D1_{[X\le x_1]}, r_1\right), K\left(\left(1-D\right)1_{[X\le x_2]}, r_2\right)\right) &= \left(r_1 \wedge r_2\right)\left(0 - \rho\left(1-\rho\right)F_D(x_1)F_{\bar{D}}(x_2)\right) \\ &= -\left(r_1 \wedge r_2\right)\rho\left(1-\rho\right)F_D(x_1)F_{\bar{D}}(x_2), \end{aligned}$$

$$\begin{aligned} Cov\left(K\left(D1_{[X\le x_1]}, r_1\right), K\left(D, r_2\right)\right) &= \left(r_1 \wedge r_2\right)\left(\rho F_D(x_1) - \rho^2 F_D(x_1)\right) \\ &= \left(r_1 \wedge r_2\right)\rho\left(1-\rho\right)F_D(x_1), \end{aligned}$$

and

$$\begin{aligned} Cov\left(K\left(\left(1-D\right)1_{[X\le x_1]}, r_1\right), K\left(D, 1_{[X\le x_2]}\right)\right) &= \left(r_1 \wedge r_2\right)\left(0 - \rho\left(1-\rho\right)F_{\bar{D}}(x_1)\right) \\ &= -\left(r_1 \wedge r_2\right)\rho\left(1-\rho\right)F_{\bar{D}}(x_1). \end{aligned}$$

Now, note that

$$\begin{aligned} n^{-1/2}[nr]\left(\hat{F}_{D,r}(x)-F_D(x)\right) =& n^{-1/2}[nr]\left(\frac{\hat{P}_r\left(X\le x,D=1\right)}{\hat{\rho}_r}-\frac{P\left(X\le x,D=1\right)}{\rho}\right)\\ =& n^{-1/2}[nr]\left(\frac{\hat{P}_r\left(X\le x,D=1\right)}{\hat{\rho}_r}-\frac{P\left(X\le x,D=1\right)}{\hat{\rho}_r}\right)\\ &+n^{-1/2}[nr]\left(\frac{P\left(X\le x,D=1\right)}{\hat{\rho}_r}-\frac{P\left(X\le x,D=1\right)}{\rho}\right)\\ =& \frac{1}{\hat{\rho}_r}n^{-1/2}[nr]\left(\hat{P}_r\left(X\le x,D=1\right)-P\left(X\le x,D=1\right)\right)\\ &-\frac{F_D(x)}{\hat{\rho}_r}n^{-1/2}[nr]\left(\hat{\rho}_r-\rho\right). \end{aligned}$$

From above we conclude

$$n^{-1/2}[nr]\left(\hat{F}_{D,r}(x)-F_D(x)\right)\rightarrow_D \frac{1}{\rho}K\left(D1_{[X\le x]},r\right)-\frac{F_D(x)}{\rho}K\left(D,r\right),$$

Similarly,

$$\begin{aligned} n^{-1/2}[nr]\left(\hat{F}_{\bar{D},r}(x)-F_{\bar{D}}(x)\right) =& n^{-1/2}[nr]\left(\frac{\hat{P}_r\left(X\le x,D=0\right)}{1-\hat{\rho}_r}-\frac{P\left(X\le x,D=0\right)}{1-\rho}\right)\\ =& n^{-1/2}[nr]\left(\frac{\hat{P}_r\left(X\le x,D=0\right)}{1-\hat{\rho}_r}-\frac{P\left(X\le x,D=0\right)}{1-\hat{\rho}_r}\right)\\ &+n^{-1/2}[nr]\left(\frac{P\left(X\le x,D=1\right)}{1-\hat{\rho}_r}-\frac{P\left(X\le x,D=1\right)}{1-\rho}\right)\\ =& \frac{1}{1-\hat{\rho}_r}n^{-1/2}[nr]\left(\hat{P}_r\left(X\le x,D=0\right)-P\left(X\le x,D=0\right)\right)\\ &+\frac{F_{\bar{D}}(x)}{1-\hat{\rho}_r}n^{-1/2}[nr]\left(\hat{\rho}_r-\rho\right), \end{aligned}$$

and

$$n^{-1/2}[nr]\left(\hat{F}_{\bar{D},r}(x)-F_{\bar{D}}(x)\right)\rightarrow_D \frac{1}{1-\rho}K\left(\left(1-D\right)1_{[X\le x]},r\right)+\frac{F_{\bar{D}}(x)}{1-\rho}K\left(D,r\right).$$

To show that the limiting processes of $n^{-1/2}[nr]\left(\hat{F}_{D,r}(x)-F_D(x)\right)$ and $n^{-1/2}[nr]\left(\hat{F}_{\bar{D},r}(x)-F_{\bar{D}}(x)\right)$ are independent we must show that $\frac{1}{\rho}K\left(D1_{[X\le x]},r\right)-\frac{F_D(x)}{\rho}K\left(D,r\right)$ and

$\frac{1}{1-\rho}K\left((1-D)\,1_{[X\leq x]},r\right)+\frac{F_{\bar{D}}(x)}{1-\rho}K\left(D,r\right)$ have covariance 0. Without loss of generality, assume $r_1 \leq r_2$,

$$\begin{aligned}
&Cov\left(\frac{1}{\rho}K\left(D1_{[X\leq x_1]},r_1\right)-\frac{F_D(x_1)}{\rho}K\left(D,r_1\right),\frac{1}{1-\rho}K\left((1-D)\,1_{[X\leq x_2]},r_2\right)+\frac{F_{\bar{D}}(x_2)}{1-\rho}K\left(D,r_2\right)\right)\\
=&\frac{1}{\rho\,(1-\rho)}Cov\left(K\left(D1_{[X\leq x_1]},r_1\right),K\left((1-D)\,1_{[X\leq x_2]},r_2\right)\right)+\frac{F_{\bar{D}}(x_2)}{\rho\,(1-\rho)}Cov\left(K\left(D1_{[X\leq x_1]},r_1\right),K\left(D,r_2\right)\right)\\
&-\frac{F_D(x_1)}{\rho\,(1-\rho)}Cov\left(K\left(D,r_1\right),K\left((1-D)\,1_{[X\leq x_2]},r_2\right)\right)-\frac{F_D(x_1)F_{\bar{D}}(x_2)}{\rho\,(1-\rho)}Cov\left(K\left(D,r_1\right),K\left(D,r_2\right)\right)\\
=&-r_1F_D(x_1)F_{\bar{D}}(x_2)+r_1F_D(x_1)F_{\bar{D}}(x_2)+r_1F_D(x_1)F_{\bar{D}}(x_2)-r_1F_D(x_1)F_{\bar{D}}(x_2)\\
=&0,
\end{aligned} \tag{10}$$

and we conclude that the limiting processes of $n^{-1/2}[nr]\left(\hat{F}_{D,r}(x)-F_D(x)\right)$ and $n^{-1/2}[nr]\left(\hat{F}_{\bar{D},r}(x)-F_{\bar{D}}(x)\right)$ are independent. A similar calculation shows that the limiting processes of $n^{-1/2}[nr]\left(\hat{F}_{D,r}(x)-F_D(x)\right)$ and $n^{-1/2}[nr]\left(\hat{\rho}_r-\rho\right)$ are independent. Again, assume $r_1 \leq r_2$,

$$\begin{aligned}
Cov\left(\frac{1}{\rho}K\left(D1_{[X\leq x]},r_1\right)-\frac{F_D(x)}{\rho}K\left(D,r_1\right),K\left(D,r_2\right)\right)=&\frac{1}{\rho}Cov\left(K\left(D1_{[X\leq x]},r_1\right),K\left(D,r_2\right)\right)-\frac{F_D(x)}{\rho}Cov\left(K\left(D,r_1\right),K\left(D,r_2\right)\right)\\
=&\frac{1}{\rho}r_1\left(\rho F_D(x)-\rho^2F_D(x_1)\right)-\frac{F_D(x)}{\rho}r_1\left(\rho-\rho^2\right)\\
=&F_D(x)r_1\,(1-\rho)-F_D(x)r_1\,(1-\rho)\\
=&0.
\end{aligned} \tag{11}$$

Finally, we can show that the limiting processes of $n^{-1/2}[nr]\left(\hat{F}_{\bar{D},r}(x)-F_{\bar{D}}(x)\right)$and $n^{-1/2}[nr]\left(\hat{\rho}_r-\rho\right)$ are independent. Again, assuming $r_1 \leq r_2$,

$$\begin{aligned}
&Cov\left(\frac{1}{1-\rho}K\left((1-D)\,1_{[X\leq x]},r_1\right)+\frac{F_{\bar{D}}(x_1)}{1-\rho}K\left(D,r_1\right),K\left(D,r_2\right)\right)\\
&=\frac{1}{1-\rho}Cov\left(K\left((1-D)\,1_{[X\leq x]},r_1\right),K\left(D,r_2\right)\right)+\frac{F_{\bar{D}}(x)}{1-\rho}Cov\left(K\left(D,r_1\right),K\left(D,r_2\right)\right)\\
&=-r_1\rho F_{\bar{D}}(x)+r_1\rho F_{\bar{D}}(x)\\
&=0,
\end{aligned} \tag{12}$$

and we conclude that the limiting processes of $n^{-1/2}[nr]\left(\hat{F}_{\bar{D},r}(x)-F_{\bar{D}}(x)\right)$ and $n^{-1/2}[nr]\left(\hat{\rho}_r-\rho\right)$ are independent.

We next show that $\frac{1}{\rho}K\left(D1_{[X\leq x]},r\right)-\frac{F_D(x)}{\rho}K\left(D,r\right)$ is equal in distribution to an (ordinary) Kiefer process indexed by $[0,1]\times[0,1]$, $\frac{1}{\sqrt{\rho}}K_3\left(F_D(x),r\right)$. $\frac{1}{\rho}K\left(D1_{[X\leq x]},r\right)-\frac{F_D(x)}{\rho}K\left(D,r\right)$ is a mean 0 Gaussian process and will be equal in distribution to $\frac{1}{\sqrt{\rho}}K_3\left(F_D(x),r\right)$ if they have the same covariance structure. Without loss of generality assume $r_1 \le r_2$ and $x_1 \le x_2$,

$$\begin{aligned}
&Cov\left(\frac{1}{\rho}K\left(D1_{[X\le x_1]},r_1\right) - \frac{F_D(x_1)}{\rho}K\left(D,r_1\right), \frac{1}{\rho}K\left(D1_{[X\le x_2]},r_2\right) - \frac{F_D(x_2)}{\rho}K\left(D,r_2\right)\right)\\
&=\frac{1}{\rho^2}Cov\left(K\left(D1_{[X\le x_1]},r_1\right), K\left(D1_{[X\le x_2]},r_2\right)\right) - \frac{F_D(x_1)}{\rho^2}Cov\left(K\left(D,r_1\right), K\left(D1_{[X\le x_2]},r_2\right)\right)\\
&\quad - \frac{F_D(x_2)}{\rho^2}Cov\left(K\left(D1_{[X\le x_1]},r_1\right), K\left(D,r_2\right)\right) + \frac{F_D(x_1)F_D(x_2)}{\rho^2}Cov\left(K\left(D,r_1\right), K\left(D,r_2\right)\right)\\
&=\frac{r_1\left(\rho F_D(x_1) - \rho^2 F_D(x_1)F_D(x_2)\right)}{\rho^2} - \frac{F_D(x_1)r_1\left(\rho F_D(x_2) - \rho^2 F_D(x_2)\right)}{\rho^2}\\
&\quad - \frac{F_D(x_2)r_1\left(\rho F_D(x_1) - \rho^2 F_D(x_1)\right)}{\rho^2} + \frac{F_D(x_1)F_D(x_2)r_1\rho\left(1-\rho\right)}{\rho^2}\\
&=\frac{r_1\left(F_D(x_1) - F_D(x_1)F_D(x_2)\right)}{\rho}\\
&=Cov\left(\frac{1}{\sqrt{\rho}}K_3\left(F_D(x_1),r_1\right), \frac{1}{\sqrt{\rho}}K_3\left(F_D(x_2),r_2\right)\right).
\end{aligned}$$

This implies,

$$\frac{1}{\rho}K\left(D1_{[X\le x]},r\right) - \frac{F_D(x)}{\rho}K\left(D,r\right) =_D \frac{1}{\sqrt{\rho}}K_3\left(F_D(x),r\right),$$

where K_3 is a Kiefer process, and

$$n^{-1/2}[nr]\left(\hat{F}_{D,r}(x) - F_D(x)\right) \to_D \frac{1}{\sqrt{\rho}}K_3\left(F_D(x),r\right). \tag{13}$$

A nearly identical argument shows that $\frac{1}{1-\rho}K\left(\left(1-D\right)1_{[X\le x]},r\right) + \frac{F_{\bar{D}}(x)}{1-\rho}K\left(D,r\right)$ is equal in distribution to an (ordinary) Kiefer process indexed by $[0,1]\times[0,1]$,
$\frac{1}{\sqrt{1-\rho}}K_4\left(F_{\bar{D}}(x),r\right)$, and we conclude

$$n^{-1/2}[nr]\left(\hat{F}_{\bar{D},r}(x) - F_{\bar{D}}(x)\right) \to_D \frac{1}{\sqrt{1-\rho}}K_4\left(F_{\bar{D}}(x),r\right). \tag{14}$$

Finally, we know that

$$K\left(D,r\right) =_D \sqrt{\rho\left(1-\rho\right)}W\left(r\right) \tag{15}$$

where W is a Wiener process. Combining (10) - (15) gives the desired result. □

Lemma 2.4 provides the joint asymptotic behavior of $n^{-1/2}[nr]\left(\hat{F}_{D,r}(x) - F_D(x)\right)$, $n^{-1/2}[nr]\left(\hat{F}_{\bar{D},r}(x) - F_{\bar{D}}(x)\right)$ and $n_{-1/2}[nr]\left(\hat{\rho}_r - \rho\right)$ under cohort sampling. This result will be used when developing asymptotic theory for the ROC, PPV and NPV curves under cohort sampling. We next provide three lemmas that deal directly with the behavior of the sequentail empirical ROC curve under cohort sampling. We begin by showing that the sequential empirical ROC curve is consistent under cohort sampling.

Lemma 2.5. *Assume A1-A3 hold and that* $\rho \in (0,1)$.

A. *As* $n \to \infty$

$$\widehat{ROC}_r(t) \to_{a.s} ROC(t)$$

uniformly for $t \in [a,b]$ *and* $r \in [e,1]$.

B. *As* $n \to \infty$

$$\widehat{ROC}_r^{-1}(v) \to_{a.s} ROC^{-1}(v)$$

uniformly for $v \in [a,b]$ *and* $r \in [e,1]$.

Proof. We begin by showing that $\hat{F}_{D,r}(x)$ converges uniformly to $F_D(x)$ for $x \in \Re$ and $r \in (e,1]$. Note that,

$$\begin{aligned}\sup_{e\le r\le 1}\sup_{x\in\Re}\left|\hat{F}_{D,r}(x)-F_D(x)\right| &= \sup_{e\le r\le 1}\sup_{x\in\Re}\left|\frac{\hat{P}_r\left(X\le x, D=1\right)}{\hat{\rho}_r}-\frac{P\left(X\le x, D=1\right)}{\rho}\right| \\ &\le \sup_{e\le r\le 1}\sup_{x\in\Re}\left|\frac{\hat{P}_r\left(X\le x, D=1\right)}{\hat{\rho}_r}-\frac{\hat{P}_r\left(X\le x, D=1\right)}{\rho}\right| \\ &\quad+\sup_{e\le r\le 1}\sup_{x\in\Re}\left|\frac{\hat{P}_r\left(X\le x, D=1\right)}{\rho}-\frac{P\left(X\le x, D=1\right)}{\rho}\right|.\end{aligned}$$

The first term can be written as

$$\begin{aligned}\sup_{e\le r\le 1}\sup_{x\in\Re}\left|\frac{\hat{P}_r\left(X\le x, D=1\right)}{\hat{\rho}_r}-\frac{\hat{P}_r\left(X\le x, D=1\right)}{\rho}\right| &= \frac{n}{[ne]}\sup_{e\le r\le 1}\sup_{x\in\Re}\frac{[ne]}{n}\left|\hat{P}_r\left(X\le x, D=1\right)\left(\frac{1}{\hat{\rho}_r}-\frac{1}{\rho}\right)\right| \\ &\le \frac{n}{[ne]}\sup_{e\le r\le 1}\sup_{x\in\Re}\frac{[nr]}{n}\left|\frac{1}{\hat{\rho}_r}-\frac{1}{\rho}\right| \\ &= \frac{n}{[ne]}\sup_{e\le r\le 1}\frac{[nr]}{n}\left|\frac{1}{\hat{\rho}_r}-\frac{1}{\rho}\right| \\ &\to_{a.s.} 0,\end{aligned}$$

where the last line is a result of the Glivenko-Cantelli theorems (Theorem 1.52 of Csörgő and Szyszkowicz

(1998)), the continuity of $\frac{1}{\rho}$ and $\frac{n}{[ne]} \to \frac{1}{e}$. The second term can be written as

$$\begin{aligned}
\sup_{e\le r\le 1}\sup_{x\in\Re}\left|\frac{\hat{P}\left(X\le x,D=1\right)}{\rho}-\frac{P\left(X\le x,D=1\right)}{\rho}\right| &= \frac{1}{\rho}\frac{n}{[ne]}\sup_{e\le r\le 1}\sup_{x\in\Re}\frac{[ne]}{n}\left|\hat{P}\left(X\le x,D=1\right)-P\left(X\le x,D=1\right)\right| \\
&\le \frac{1}{\rho}\frac{n}{[ne]}\sup_{e\le r\le 1}\sup_{x\in\Re}\frac{[nr]}{n}\left|\hat{P}\left(X\le x,D=1\right)-P\left(X\le x,D=1\right)\right| \\
&\to_{a.s}0.
\end{aligned}$$

Again, the last line is a result of the Glivenko-Cantelli theorems and $\frac{n}{[ne]} \to \frac{1}{e}$. Combining these two results gives us

$$\sup_{e\le r\le 1}\sup_{x\in\Re}\left|\hat{F}_{D,r}(x)-F_D(x)\right| \to_{a.s.} 0. \tag{16}$$

Furthermore, we have

$$\begin{aligned}
\sup_{e\le r\le 1}\sup_{a\le t\le b}\left|F_D\left(\hat{F}_D^{-1}(t)\right)-t\right| \le& \sup_{e\le r\le 1}\sup_{a\le t\le b}\left|F_D\left(\hat{F}_D^{-1}(t)\right)-\hat{F}_D\left(\hat{F}_D^{-1}(t)\right)\right| \\
&+\sup_{e\le r\le 1}\sup_{a\le t\le b}\left|\hat{F}_D\left(\hat{F}_D^{-1}(t)\right)-t\right|.
\end{aligned}$$

We know that,

$$\sup_{e\le r\le 1}\sup_{a\le t\le b}\left|F_D\left(\hat{F}_D^{-1}(t)\right)-\hat{F}_D\left(\hat{F}_D^{-1}(t)\right)\right| \to_{a.s.} 0,$$

by (16) and

$$\sup_{e\le r\le 1}\sup_{a\le t\le b}\left|\hat{F}_D\left(\hat{F}_D^{-1}(t)\right)-t\right| \le_{a.s.} \frac{1}{\sum_{i=1}^{[ne]}D_i} \to 0.$$

Combining these two results gives us

$$\sup_{e\le r\le 1}\sup_{a\le t\le b}\left|F_D\left(\hat{F}_D^{-1}(t)\right)-t\right| \to_{a.s.} 0. \tag{17}$$

Returning to the *ROC* curve under cohort sampling, we have

$$\begin{aligned}\sup_{e\le r\le 1}\sup_{a\le t\le b}\left|\hat{S}_{D,r}\left(\hat{S}^{-1}_{\bar{D},r}(t)\right)-S_D\left(S^{-1}_{\bar{D}}(t)\right)\right| &\le \sup_{e\le r\le 1}\sup_{a\le t\le b}\left|\hat{S}_{D,r}\left(\hat{S}^{-1}_{\bar{D},r}(t)\right)-S_D\left(\hat{S}^{-1}_{\bar{D},r}(t)\right)\right| \\ &\quad+\sup_{e\le r\le 1}\sup_{a\le t\le b}\left|S_D\left(\hat{S}^{-1}_{\bar{D},r}(t)\right)-S_D\left(S^{-1}_{\bar{D}}(t)\right)\right| \\ &=\sup_{e\le r\le 1}\sup_{a\le t\le b}\left|\hat{S}_{D,r}\left(\hat{S}^{-1}_{\bar{D},r}(t)\right)-S_D\left(\hat{S}^{-1}_{\bar{D},r}(t)\right)\right| \\ &\quad+\sup_{e\le r\le 1}\sup_{a\le t\le b}\left|S_D\left(S^{-1}_{\bar{D}}\left(S_{\bar{D}}\left(\hat{S}^{-1}_{\bar{D},r}(t)\right)\right)\right)-S_D\left(S^{-1}_{\bar{D}}(t)\right)\right|\end{aligned}$$

The first term coverges to 0 uniformly as a result of (16), while the second term converges uniformly to 0 as a result of (17) and the uniform continuity of $S_D\left(S^{-1}_{\bar{D}}(t)\right)$. Combining these two results gives us

$$\sup_{e\le r\le 1}\sup_{a\le t\le b}\left|\hat{S}_{D,r}\left(\hat{S}^{-1}_{\bar{D},r}(t)\right)-S_D\left(S^{-1}_{\bar{D}}(t)\right)\right|\to_{a.s.} 0$$

The proof of part B is nearly identical. □

The consistency of the sequential empirical ROC curve under cohort sampling will be used in the remaining sections of this chapter when developing asymptotic theory for the sequential empirical PPV and NPV curves. The following lemma provides asymptotic theory for the sequential empirical ROC curve under cohort sampling.

Lemma 2.6. *Assume A1-A3 hold.*

A. Let $\frac{f_D(S^{-1}_{\bar{D}}(t))}{f_{\bar{D}}(S^{-1}_{\bar{D}}(t))}$ be bounded on $[a,b]$. As $n\to\infty$

$$n^{-1/2}[nr](\widehat{ROC}_r(t)-ROC(t))\to_D \frac{1}{\sqrt{\rho}}K_3(ROC(t),r)+\left(\frac{f_D(S^{-1}_{\bar{D}}(t))}{f_{\bar{D}}(S^{-1}_{\bar{D}}(t))}\right)\frac{1}{\sqrt{1-\rho}}K_4(t,r)$$

uniformly for $t\in[a,b]$ and $r\in[e,1]$ where K_3 and K_4 are independent Kiefer Processes.

B. Let $\frac{f_{\bar{D}}(S^{-1}_{D}(v))}{f_{D}(S^{-1}_{D}(v))}$ be bounded on $[a,b]$. As $n\to\infty$

$$n^{-1/2}[nr](\widehat{ROC}^{-1}_r(v)-ROC^{-1}(v))\to_D \frac{1}{\sqrt{1-\rho}}K_4(ROC^{-1}(v),r)+\left(\frac{f_{\bar{D}}(S^{-1}_{D}(v))}{f_{D}(S^{-1}_{D}(v))}\right)\frac{1}{\sqrt{\rho}}K_3(v,r)$$

uniformly for $v\in[a,b]$ and $r\in[e,1]$ where K_3 and K_4 are independent Kiefer Processes.

Proof. We provide a proof for part A and note that the proof of part B is nearly identical. First,

$$\begin{aligned} n^{-1/2}[nr](R\hat{O}C_r(t) - ROC(t)) =& n^{-1/2}[nr]\left(\hat{S}_{D,r}(\hat{S}^{-1}_{\bar{D},r}(t)) - S_D(S^{-1}_{\bar{D}}(t))\right) \\ =& n^{-1/2}[nr]\left(\hat{S}_{D,r}(\hat{S}^{-1}_{\bar{D},r}(t)) - S_D(\hat{S}^{-1}_{\bar{D},r_{\bar{D}}}(t))\right) \\ &+ n^{-1/2}[nr]\left(S_D(\hat{S}^{-1}_{\bar{D},r}(t)) - S_D(S^{-1}_{\bar{D}}(t))\right). \end{aligned}$$

We know that $S_{\bar{D}}\left(\hat{S}^{-1}_{\bar{D},r}(t)\right)$ converges uniformly to t by (17). This, combined with the uniform continuity of $S^{-1}_{\bar{D}}(t)$, allows us to conclude,

$$\sup_{e\le r\le 1}\sup_{a\le t\le b}\left|\hat{S}^{-1}_{\bar{D}}(t) - S^{-1}_{\bar{D}}(t)\right| \to_{a.s.} 0.$$

Lemma 2.4, the uniform convergence of $\hat{S}^{-1}_{\bar{D}}(t)$ to $S^{-1}(t)$ for $t \in [a,b]$ and $r \in [e,1]$ and the uniform continuity of the Kiefer process gives us,

$$n^{-1/2}[nr]\left(\hat{S}_{D,r}(\hat{S}^{-1}_{\bar{D},r}(t)) - S_D(S^{-1}_{\bar{D}}(t))\right) \to_D \frac{1}{\sqrt{\rho}}K_3(ROC(t), r), \tag{18}$$

uniformly for $t \in [a,b]$ and $r \in [e,1]$.

The second term can be re-written as,

$$\begin{aligned} & n^{-1/2}[nr]\left(S_D(\hat{S}^{-1}_{\bar{D},r}(t)) - S_D(S^{-1}_{\bar{D}}(t))\right) \\ =& n^{-1/2}[nr]\left(S_D\left(S^{-1}_{\bar{D}}\left(S_{\bar{D}}\left(\hat{S}^{-1}_{\bar{D},r}(t)\right)\right)\right) - S_D\left(S^{-1}_{\bar{D}}(t)\right)\right) \\ =& \frac{\left(S_D\left(S^{-1}_{\bar{D}}\left(S_{\bar{D}}\left(\hat{S}^{-1}_{\bar{D},r}(t)\right)\right)\right) - S_D\left(S^{-1}_{\bar{D}}(t)\right)\right)}{S_{\bar{D}}\left(\hat{S}^{-1}_{\bar{D},r}(t)\right) - t} n^{-1/2}[nr]\left(S_{\bar{D}}\left(\hat{S}^{-1}_{\bar{D},r}(t)\right) - t\right) \\ =& \frac{\left(S_D\left(S^{-1}_{\bar{D}}\left(S_{\bar{D}}\left(\hat{S}^{-1}_{\bar{D},r}(t)\right)\right)\right) - S_D\left(S^{-1}_{\bar{D}}(t)\right)\right)}{S_{\bar{D}}\left(\hat{S}^{-1}_{\bar{D},r}(t)\right) - t} n^{-1/2}[nr]\left(S_{\bar{D}}\left(\hat{S}^{-1}_{\bar{D},r}(t)\right) - \hat{S}_{\bar{D},r}\left(\hat{S}^{-1}_{\bar{D},r}(t)\right)\right) \\ &+ \frac{\left(S_D\left(S^{-1}_{\bar{D}}\left(S_{\bar{D}}\left(\hat{S}^{-1}_{\bar{D},r}(t)\right)\right)\right) - S_D\left(S^{-1}_{\bar{D}}(t)\right)\right)}{S_{\bar{D}}\left(\hat{S}^{-1}_{\bar{D},r}(t)\right) - t} n^{-1/2}[nr]\left(\hat{S}_{\bar{D},r}\left(\hat{S}^{-1}_{\bar{D},r}(t)\right) - t\right). \end{aligned}$$

By the mean value theorem, there exists a $S_{\bar{D}}\left(\tilde{S}^{-1}_{\bar{D},r}(t)\right)$ between $S_{\bar{D}}\left(\hat{S}^{-1}_{\bar{D},r}(t)\right)$ and t such that,

$$\frac{S_D\left(S_{\bar{D}}^{-1}\left(S_{\bar{D}}\left(\hat{S}^{-1}_{\bar{D},r}(t)\right)\right)\right)-S_D\left(S_{\bar{D}}^{-1}(t)\right)}{S_{\bar{D}}\left(\hat{S}^{-1}_{\bar{D},r}(t)\right)-t}=\frac{f_D\left(S_{\bar{D}}^{-1}\left(S_{\bar{D}}\left(\tilde{S}^{-1}_{\bar{D},r}(t)\right)\right)\right)}{f_{\bar{D}}\left(S_{\bar{D}}^{-1}\left(S_{\bar{D}}\left(\tilde{S}^{-1}_{\bar{D},r}(t)\right)\right)\right)}.$$

From (17), we know that $S_{\bar{D}}\left(\hat{S}^{-1}_{\bar{D},r}(t)\right)\rightarrow_{a.s.} t$, uniformly for $t\in[a,b]$ and $r\in[e,1]$, and, therefore, $S_{\bar{D}}\left(\tilde{S}^{-1}_{\bar{D},r}(t)\right)\rightarrow_{a.s.} t$, uniformly for $t\in[a,b]$ and $r\in[e,1]$. This, along with the uniform continuity of $\frac{f_D\left(S_{\bar{D}}^{-1}(t)\right)}{f_{\bar{D}}\left(S_{\bar{D}}^{-1}(t)\right)}$, allows us to conclude that,

$$\sup_{e\leq r\leq 1}\sup_{a\leq t\leq b}\left|\frac{f_D\left(S_{\bar{D}}^{-1}\left(S_{\bar{D}}\left(\tilde{S}^{-1}_{\bar{D},r}(t)\right)\right)\right)}{f_{\bar{D}}\left(S_{\bar{D}}^{-1}\left(S_{\bar{D}}\left(\tilde{S}^{-1}_{\bar{D},r}(t)\right)\right)\right)}-\frac{f_D\left(S_{\bar{D}}^{-1}(t)\right)}{f_{\bar{D}}\left(S_{\bar{D}}^{-1}(t)\right)}\right|\rightarrow_{a.s.} 0,$$

which implies,

$$\sup_{e\leq r\leq 1}\sup_{a\leq t\leq b}\left|\frac{S_D\left(S_{\bar{D}}^{-1}\left(S_{\bar{D}}\left(\hat{S}^{-1}_{\bar{D},r}(t)\right)\right)\right)-S_D\left(S_{\bar{D}}^{-1}(t)\right)}{S_{\bar{D}}\left(\hat{S}^{-1}_{\bar{D},r}(t)\right)-t}-\frac{f_D\left(S_{\bar{D}}^{-1}(t)\right)}{f_{\bar{D}}\left(S_{\bar{D}}^{-1}(t)\right)}\right|\rightarrow_{a.s.} 0. \tag{19}$$

Furthermore,

$$\sup_{e\leq r\leq 1}\sup_{a\leq t\leq b} n^{-1/2}[nr]\left|\hat{S}_{\bar{D},r}\left(\hat{S}^{-1}_{\bar{D},r}(t)\right)-t\right|\leq_{a.s.}\frac{n^{1/2}}{\sum_{i=1}^{[ne]}D_i},$$

and

$$\sup_{e\leq r\leq 1}\sup_{a\leq t\leq b} n^{-1/2}[nr]\left|\hat{S}_{\bar{D},r}\left(\hat{S}^{-1}_{\bar{D},r}(t)\right)-t\right|\rightarrow_{a.s.} 0. \tag{20}$$

By Lemma 2.4, the uniform convergence of $\hat{S}_{\bar{D}}^{-1}(t)$ to $S^{-1}(t)$ for $t\in[a,b]$ and $r\in[e,1]$ and the uniform continuity of the Kiefer process we conclude,

$$n^{-1/2}[nr]\left(S_{\bar{D}}\left(\hat{S}^{-1}_{\bar{D},r}(t)\right)-\hat{S}_{\bar{D},r}\left(\hat{S}^{-1}_{\bar{D},r}(t)\right)\right)\rightarrow_D\frac{1}{\sqrt{1-\rho}}K_4(t,r), \tag{21}$$

uniformly for $t\in[a,b]$ and $r\in[e,1]$. Combining (19), (20) and (21) allows us to conclude,

$$n^{-1/2}[nr]\left(S_D(\hat{S}^{-1}_{\bar{D},r}(t))-S_D(S_{\bar{D}}^{-1}(t))\right)\rightarrow_D\left(\frac{f_D(S_{\bar{D}}^{-1}(t))}{f_{\bar{D}}(S_{\bar{D}}^{-1}(t))}\right)\frac{1}{\sqrt{1-\rho}}K_4(t,r), \tag{22}$$

uniformly for $t\in[a,b]$ and $r\in[e,1]$. Summing (18) and (22) gives the desired result. □

Lemma 2.6 will be used in the next three sections to develop asymptotic theory for the empirical PPV and NPV curves under cohort sampling. The final Lemma of this section provides asymptotic theory for the sequential empirical estimate of a point on the ROC curve under cohort sampling.

Lemma 2.7. *Assume A1-A3 hold.*

A. *Let* $\frac{f_D(S_{\bar{D}}^{-1}(t))}{f_{\bar{D}}(S_{\bar{D}}^{-1}(t))}$ *be bounded on* $[a,b]$*. For* $t \in (0,1)$ *and J stopping times,* $\left(\widehat{ROC}_{r_1}(t), \widehat{ROC}_{r_2}(t), \ldots, \widehat{ROC}_{r_J}(t)\right)$*, is approximately multivariate normal with,*

$$\widehat{ROC}_{r_i}(t) \sim N\left(ROC(t), \sigma^2_{\widehat{ROC}_{r_i}(t)}\right) \qquad i = 1, 2, \ldots, J$$

and

$$Cov\left[\widehat{ROC}_{r_i}(t), \widehat{ROC}_{r_j}(t)\right] = Var\left[\widehat{ROC}_{r_j}(t)\right] = \sigma^2_{\widehat{ROC}_{r_j}(t)}, \qquad r_i \le r_j$$

where

$$\sigma^2_{\widehat{ROC}_{r_j}(t)} = \frac{ROC(t)\left(1 - ROC(t)\right)}{\rho n r_j} + \left(\frac{f_D(S_{\bar{D}}^{-1}(t))}{f_{\bar{D}}(S_{\bar{D}}^{-1}(t))}\right)^2 \frac{t\,(1-t)}{(1-\rho)\, n r_j}.$$

B. *Let* $\frac{f_{\bar{D}}(S_D^{-1}(v))}{f_D(S_D^{-1}(v))}$ *be bounded on* $[a,b]$*. For* $v \in (0,1)$ *and J stopping times,* $\left(\widehat{ROC}_{r_1}^{-1}(v), \widehat{ROC}_{r_2}^{-1}(v), \ldots, \widehat{ROC}_{r_J}^{-1}(v)\right)$*, is approximately multivariate normal with,*

$$\widehat{ROC}_{r_i}^{-1}(v) \sim N\left(ROC^{-1}(v), \sigma^2_{\widehat{ROC}_{r_i}^{-1}(v)}\right) \qquad i = 1, 2, \ldots, J$$

and

$$Cov\left[\widehat{ROC}_{r_i}^{-1}(v), \widehat{ROC}_{r_j}^{-1}(v)\right] = Var\left[\widehat{ROC}_{r_j}^{-1}(v)\right] = \sigma^2_{\widehat{ROC}_{r_j}^{-1}(v)}, \qquad r_i \le r_j$$

where

$$\sigma^2_{\widehat{ROC}_{r_j}^{-1}(v)} = \frac{ROC^{-1}(v)\left(1 - ROC^{-1}(v)\right)}{(1-\rho)\, n r_j} + \left(\frac{f_{\bar{D}}(S_D^{-1}(v))}{f_D(S_D^{-1}(v))}\right)^2 \frac{v\,(1-v)}{\rho n r_j}.$$

Proof. Immediate from Lemma 2.6. □

3 PPV and NPV curve indexed by the False Positive Fraction

We first consider the PPV and NPV curves indexed by the false positive fraction, t. In this case, the PPV and NPV curves are defined as $PPV(t) = P[D = 1|X > S_{\bar{D}}^{-1}(t)]$ and $NPV(t) = P[D = 0|X \leq S_{\bar{D}}^{-1}(t)]$ for all $t \in (0, 1)$. Under this indexing, the PPV and NPV curves can be written as functions of the ROC curve

$$\begin{aligned} PPV(t) =& P[D = 1|X > S_{\bar{D}}^{-1}(t)] \\ =& \frac{P[D = 1, X > S_{\bar{D}}^{-1}(t)]}{P[X > S_{\bar{D}}^{-1}(t)]} \\ =& \frac{P[X > S_{\bar{D}}^{-1}(t)|D = 1]P[D = 1]}{P[X > S_{\bar{D}}^{-1}(t)|D = 1]P[D = 1] + P[X > S_{\bar{D}}^{-1}(t)|D = 0]P[D = 0]} \\ =& \frac{ROC\,(t)\,\rho}{ROC\,(t)\,\rho + t\,(1-\rho)}. \end{aligned} \tag{23}$$

and

$$NPV(t) = \frac{(1-t)\,(1-\rho)}{(1 - ROC\,(t))\,\rho + (1-t)\,(1-\rho)}. \tag{24}$$

The sequential empirical estimates of $PPV(t)$ and $NPV(t)$ can be found be plugging the sequential empirical estimate of $ROC(t)$ into (23) and (24). It is straight-forward to derive asymptotic theory for $PPV(t)$ and $NPV(t)$ using the results from Section 2.

3.1 Under Case-Control Sampling

Consider estimation of $PPV(t)$ and $NPV(t)$ under case-control sampling. In case-control sampling, we sample a pre-specified number of cases and controls and assume that the prevalence is known. The sequential empirical estimates of $PPV(t)$ and $NPV(t)$ can be found by substituting the sequential empirical estimate of $ROC(t)$ into (23) and (24). The sequential empirical estimates of $PPV(t)$ and $NPV(t)$ are therefore defined as

$$\widehat{PPV}_{cc,r_D,r_{\bar{D}}}(t) = \frac{\widehat{ROC}_{r_D,r_{\bar{D}}}\,(t)\,\rho}{\widehat{ROC}_{r_D,r_{\bar{D}}}\,(t)\,\rho + t\,(1-\rho)},$$

and

$$\widehat{NPV}_{cc,r_D,r_{\bar{D}}}(t) = \frac{(1-t)\,(1-\rho)}{\left(1-\widehat{ROC}_{r_D,r_{\bar{D}}}(t)\right)\rho + (1-t)\,(1-\rho)}.$$

We see that $\widehat{PPV}_{cc,r_D,r_{\bar{D}}}(t)$ and $\widehat{NPV}_{cc,r_D,r_{\bar{D}}}(t)$ are functions of $\widehat{ROC}_{r_D,r_{\bar{D}}}(t)$ and therefore we can use the results from Section 2 to derive asymptotic theory for $\widehat{PPV}_{cc,r_D,r_{\bar{D}}}(t)$ and $\widehat{NPV}_{cc,r_D,r_{\bar{D}}}(t)$. Theorem 3.1 establishes that $\widehat{PPV}_{cc,r_D,r_{\bar{D}}}(t)$ and $\widehat{NPV}_{cc,r_D,r_{\bar{D}}}(t)$ both converge to the sum of two independent Kiefer Proccesses.

Theorem 3.1. *Assume A1-A4 hold and let* $\frac{f_D(S_{\bar{D}}^{-1}(t))}{f_{\bar{D}}(S_{\bar{D}}^{-1}(t))}$ *be bounded on* $[a,b]$.

A. As $n_D \to \infty$ *and* $n_{\bar{D}} \to \infty$

$$n_D^{-1/2}[n_D r_D](\widehat{PPV}_{cc,r_D,r_{\bar{D}}}(t) - PPV(t)) \to_D \left(\frac{t\,(1-\rho)\,\rho}{(ROC(t)\rho + t\,(1-\rho))^2}\right) K_1(ROC(t), r_D) + \left(\frac{t\,(1-\rho)\,\rho}{(ROC(t)\rho + t\,(1-\rho))^2}\right)\lambda^{1/2}\frac{r_D}{r_{\bar{D}}}\left(\frac{f_D(S_{\bar{D}}^{-1}(t))}{f_{\bar{D}}(S_{\bar{D}}^{-1}(t))}\right) K_2(t, r_{\bar{D}})$$

uniformly for $t \in [a,b]$*,* $r_D \in [c,1]$ *and* $r_{\bar{D}} \in [d,1]$ *where* K_1 *and* K_2 *are independent Kiefer Processes.*

B. As $n_D \to \infty$ *and* $n_{\bar{D}} \to \infty$

$$n_D^{-1/2}[n_D r_D](\widehat{NPV}_{cc,r_D,r_{\bar{D}}}(t) - NPV(t)) \to_D \left(\frac{(1-t)\,(1-\rho)\,\rho}{((1-ROC(t))\,\rho + (1-t)\,(1-\rho))^2}\right) K_1(ROC(t), r_D) + \left(\frac{(1-t)\,(1-\rho)\,\rho}{((1-ROC(t))\,\rho + (1-t)\,(1-\rho))^2}\right)\lambda^{1/2}\frac{r_D}{r_{\bar{D}}}\left(\frac{f_D(S_{\bar{D}}^{-1}(t))}{f_{\bar{D}}(S_{\bar{D}}^{-1}(t))}\right) K_2(t, r_{\bar{D}})$$

uniformly for $t \in [a,b]$*,* $r_D \in [c,1]$ *and* $r_{\bar{D}} \in [d,1]$ *where* K_1 *and* K_2 *are independent Kiefer Processes.*

Proof. Again, we present a proof for part A and note the proof of B is nearly identical. First, note that

$$\begin{aligned}
&n_D^{-1/2}[n_D r_D]\left(\widehat{PPV}_{cc,r_D,r_{\bar{D}}}(t) - PPV(t)\right) \\
&\quad = n_D^{-1/2}[n_D r_D]\left(\frac{\widehat{ROC}_{r_D,r_{\bar{D}}}(t)\rho}{\widehat{ROC}_{r_D,r_{\bar{D}}}(t)\rho + t\,(1-\rho)} - \frac{ROC(t)\rho}{ROC(t)\rho + t\,(1-\rho)}\right) \\
&\quad = \frac{\left(\frac{\widehat{ROC}_{r_D,r_{\bar{D}}}(t)\rho}{\widehat{ROC}_{r_D,r_{\bar{D}}}(t)\rho + t(1-\rho)} - \frac{ROC(t)\rho}{ROC(t)\rho + t(1-\rho)}\right)}{\widehat{ROC}_{r_D,r_{\bar{D}}}(t) - ROC(t)} n_D^{-1/2}[n_D r_D]\left(\widehat{ROC}_{r_D,r_{\bar{D}}}(t) - ROC(t)\right).
\end{aligned}$$

We begin by showing that $\widehat{ROC}_{r_D,r_{\bar{D}}}(t) \rightarrow_{a.s.} ROC(t)$ uniformly for $t \in [a,b]$, $r_D \in [c,1]$ and $r_{\bar{D}} \in [d,1]$,

$$\begin{aligned}
&\sup_{c\le r_D\le 1}\sup_{d\le r_{\bar{D}}\le 1}\sup_{a\le t\le b}\left|\widehat{ROC}_{r_D,r_{\bar{D}}}(t)-ROC(t)\right| \\
&= \sup_{c\le r_D\le 1}\sup_{d\le r_{\bar{D}}\le 1}\sup_{a\le t\le b}\left|\hat{S}_{D,r_D}\left(\hat{S}^{-1}_{\bar{D},r_{\bar{D}}}(t)\right)-S_D\left(S^{-1}_{\bar{D}}(t)\right)\right| \\
&\le \sup_{c\le r_D\le 1}\sup_{d\le r_{\bar{D}}\le 1}\sup_{a\le t\le b}\left|\hat{S}_{D,r_D}\left(\hat{S}^{-1}_{\bar{D},r_{\bar{D}}}(t)\right)-S_D\left(\hat{S}^{-1}_{\bar{D},r_{\bar{D}}}(t)\right)\right| \\
&\quad + \sup_{c\le r_D\le 1}\sup_{d\le r_{\bar{D}}\le 1}\sup_{a\le t\le b}\left|S_D\left(\hat{S}^{-1}_{\bar{D},r_{\bar{D}}}(t)\right)-S_D\left(S^{-1}_{\bar{D}}(t)\right)\right| \\
&= \frac{n_D}{[n_D c]}\sup_{c\le r_D\le 1}\sup_{d\le r_{\bar{D}}\le 1}\sup_{a\le t\le b}\frac{[n_D c]}{n_D}\left|\hat{S}_{D,r_D}\left(\hat{S}^{-1}_{\bar{D},r_{\bar{D}}}(t)\right)-S_D\left(\hat{S}^{-1}_{\bar{D},r_{\bar{D}}}(t)\right)\right| \\
&\quad + \frac{n_{\bar{D}}}{[n_{\bar{D}} d]}\sup_{d\le r_{\bar{D}}\le 1}\sup_{a\le t\le b}\frac{[n_{\bar{D}} d]}{n_{\bar{D}}}\left|S_D\left(S^{-1}_{\bar{D}}\left(S_{\bar{D}}\left(\hat{S}^{-1}_{\bar{D},r_{\bar{D}}}(t)\right)\right)\right)-S_D\left(S^{-1}_{\bar{D}}\left(S_{\bar{D}}\left(S^{-1}_{\bar{D}}(t)\right)\right)\right)\right| \\
&\le \frac{n_D}{[n_D c]}\sup_{c\le r_D\le 1}\sup_{d\le r_{\bar{D}}\le 1}\sup_{a\le t\le b}\frac{[n_D r_D]}{n_D}\left|\hat{S}_{D,r_D}\left(\hat{S}^{-1}_{\bar{D},r_{\bar{D}}}(t)\right)-S_D\left(\hat{S}^{-1}_{\bar{D},r_{\bar{D}}}(t)\right)\right| \\
&\quad + \frac{n_{\bar{D}}}{[n_{\bar{D}} d]}\sup_{d\le r_{\bar{D}}\le 1}\sup_{a\le t\le b}\frac{[n_{\bar{D}} r_{\bar{D}}]}{n_{\bar{D}}}\left|S_D\left(S^{-1}_{\bar{D}}\left(S_{\bar{D}}\left(\hat{S}^{-1}_{\bar{D},r_{\bar{D}}}(t)\right)\right)\right)-S_D\left(S^{-1}_{\bar{D}}\left(S_{\bar{D}}\left(S^{-1}_{\bar{D}}(t)\right)\right)\right)\right|,
\end{aligned}$$

The Glivenko-Cantelli Theorems (1.51 and 1.52 in Csörgő and Szyszkowicz (1998)), along with the fact that $\frac{n_D}{[n_D c]} \rightarrow \frac{1}{c}$ and $\frac{n_{\bar{D}}}{[n_{\bar{D}} d]} \rightarrow \frac{1}{d}$ as $n_D \rightarrow \infty$ and $n_{\bar{D}} \rightarrow \infty$, respectively, allow us to conclude that,

$$\frac{n_D}{[n_D c]}\sup_{c\le r_D\le 1}\sup_{d\le r_{\bar{D}}\le 1}\sup_{a\le t\le b}\frac{[n_D r_D]}{n_D}\left|\hat{S}_{D,r_D}\left(\hat{S}^{-1}_{\bar{D},r_{\bar{D}}}(t)\right)-S_D\left(\hat{S}^{-1}_{\bar{D},r_{\bar{D}}}(t)\right)\right| \rightarrow_{a.s} 0,$$

and

$$\frac{n_{\bar{D}}}{[n_{\bar{D}} d]}\sup_{d\le r_{\bar{D}}\le 1}\sup_{a\le t\le b}\frac{[n_{\bar{D}} r_{\bar{D}}]}{n_{\bar{D}}}\left|S_D\left(S^{-1}_{\bar{D}}\left(S_{\bar{D}}\left(\hat{S}^{-1}_{\bar{D},r_{\bar{D}}}(t)\right)\right)\right)-S_D\left(S^{-1}_{\bar{D}}\left(S_{\bar{D}}\left(S^{-1}_{\bar{D}}(t)\right)\right)\right)\right| \rightarrow_{a.s.} 0,$$

where the second statement also relies on the uniform continuity of $S_D\left(S^{-1}_{\bar{D}}(t)\right)$. Combining the two previous results gives us

$$\sup_{c\le r_D\le 1}\sup_{d\le r_{\bar{D}}\le 1}\sup_{a\le t\le b}\left|\widehat{ROC}_{r_D,r_{\bar{D}}}(t)-ROC(t)\right| \rightarrow_{a.s} 0. \tag{25}$$

By the Mean Value Theorem, there exists a $\widetilde{ROC}(t)_{r_D,r_{\bar{D}}}$ between $\widehat{ROC}_{r_D,r_{\bar{D}}}(t)$ and $ROC(t)$ such that

$$\frac{\left(\frac{\widehat{ROC}_{r_D,r_{\bar{D}}}(t)\rho}{\widehat{ROC}_{r_D,r_{\bar{D}}}(t)\rho+t(1-\rho)}-\frac{ROC(t)\rho}{ROC(t)\rho+t(1-\rho)}\right)}{\widehat{ROC}_{r_D,r_{\bar{D}}}(t)-ROC(t)} = \frac{t(1-\rho)\rho}{\left(\widetilde{ROC}(t)_{r_D,r_{\bar{D}}}\rho+t(1-\rho)\right)^2}.$$

From (25) we know that $\widetilde{ROC}(t)_{r_D,r_{\bar{D}}} \rightarrow_{a.s.} ROC(t)$. This, combined with the uniform continuity of

$\frac{t(1-\rho)\rho}{(ROC(t)\rho+t(1-\rho))^2}$, allows us to conclude

$$\sup_{c\le r_D\le 1}\sup_{d\le r_{\bar D}\le 1}\sup_{a\le t\le b}\left|\frac{t\,(1-\rho)\,\rho}{\left(\widetilde{ROC}(t)_{r_D,r_{\bar D}}\rho+t\,(1-\rho)\right)^2}-\frac{t\,(1-\rho)\,\rho}{\left(ROC(t)\rho+t\,(1-\rho)\right)^2}\right|\to_{a.s.}0,$$

which implies

$$\frac{\left(\frac{\widehat{ROC}_{r_D,r_{\bar D}}(t)\rho}{\widehat{ROC}_{r_D,r_{\bar D}}(t)\rho+t(1-\rho)}-\frac{ROC(t)\rho}{ROC(t)\rho+t(1-\rho)}\right)}{\widehat{ROC}_{r_D,r_{\bar D}}(t)-ROC(t)}\to_{a.s.}\frac{t\,(1-\rho)\,\rho}{\left(ROC(t)\rho+t\,(1-\rho)\right)^2},\tag{26}$$

uniformly for $t\in[a,b]$, $r_D\in[c,1]$ and $r_{\bar D}\in[d,1]$. Combining (26) with the results from Theorem 2.1 gives the desired result. □

Theorem 3.1 establishes the convergence of $PPV_{cc,r_D,r_{\bar D}}(t)$ and $NPV_{cc,r_D,r_{\bar D}}(t)$ to the sum of two independent Kiefer Processes. An analagous result is not currently available for fixed-sample empirical estimates of $PPV(t)$ and $NPV(t)$ under case-control sampling. Corollary 3.2 provides such a result as a special case of Theorem 3.1.

Corollary 3.2. *Assume A1-A4 hold and let* $\frac{f_D(S_{\bar D}^{-1}(t))}{f_{\bar D}(S_{\bar D}^{-1}(t))}$ *be bounded on* $[a,b]$.

A. *As* $n_D\to\infty$ *and* $n_{\bar D}\to\infty$

$$n_D^{1/2}(\widehat{PPV}_{cc,1,1}(t)-PPV(t))\to_D\left(\frac{t\,(1-\rho)\,\rho}{(ROC(t)\rho+t\,(1-\rho))^2}\right)B_1(ROC(t))+\left(\frac{t\,(1-\rho)\,\rho}{(ROC(t)\rho+t\,(1-\rho))^2}\right)\lambda^{1/2}\left(\frac{f_D(S_{\bar D}^{-1}(t))}{f_{\bar D}(S_{\bar D}^{-1}(t))}\right)B_2(t)$$

uniformly for $t\in[a,b]$ *where* B_1 *and* B_2 *are independent Brownian Bridges.*

B. *As* $n_D\to\infty$ *and* $n_{\bar D}\to\infty$

$$n_D^{1/2}(\widehat{NPV}_{cc,1,1}(t)-NPV(t))\to_D\left(\frac{(1-t)\,(1-\rho)\,\rho}{((1-ROC(t))\,\rho+(1-t)\,(1-\rho))^2}\right)B_1(ROC(t))+\left(\frac{(1-t)\,(1-\rho)\,\rho}{((1-ROC(t))\,\rho+(1-t)\,(1-\rho))^2}\right)\lambda^{1/2}\left(\frac{f_D(S_{\bar D}^{-1}(t))}{f_{\bar D}(S_{\bar D}^{-1}(t))}\right)B_2(t)$$

uniformly for $t\in[a,b]$ *where* B_1 *and* B_2 *are independent Brownian Bridges.*

Proof. Immediate from Theorem 3.1 and by noting that $K(t,1) =_D B(t)$. $\square$

We are able to develop distribution theory for summary measures of the PPV and NPV curves using the results from Theorem 3.1 and Corollary 3.2. The PPV curve is usually summarized by $PPV(t)$, a point on the positive predictive value curve, which can be interpreted as the positive predictive value corresponding to a specificity of $1-t$. Similarly, the NPV curve is typically summarized by $NPV(t)$, a point on the NPV curve. In Corollary 3.3 we show that the sequential empirical estimate of a point on the PPV or NPV curve is asymptotically normal with an independent increments covariance structure, while Corollary 3.4 establishes the asymptotic normality of the fixed-sample empirical estimate of a point on the PPV or NPV curve as a special case.

Corollary 3.3. *Assume A1-A4 hold and let* $\frac{f_D(S_{\bar{D}}^{-1}(t))}{f_{\bar{D}}(S_{\bar{D}}^{-1}(t))}$ *be bounded on* $[a,b]$. *For* $t \in (0,1)$ *and* J *stopping times,*

A. $\left(\widehat{PPV}_{cc,r_{D,1},r_{\bar{D},1}}(t), \widehat{PPV}_{cc,r_{D,2},r_{\bar{D},2}}(t), \ldots, \widehat{PPV}_{cc,r_{D,J},r_{\bar{D},J}}(t)\right)$, *is approximately multivariate normal with,*

$$\widehat{PPV}_{cc,r_{D,i},r_{\bar{D},i}}(t) \sim N\left(PPV(t), \sigma^2_{\widehat{PPV}_{cc,r_{D,i},r_{\bar{D},i}}(t)}\right) \qquad i = 1,2,\ldots,J$$

and

$$Cov\left[\widehat{PPV}_{cc,r_{D,i},r_{\bar{D},i}}(t), \widehat{PPV}_{cc,r_{D,j},r_{\bar{D},j}}(t)\right] = Var\left[\widehat{PPV}_{cc,r_{D,j},r_{\bar{D},j}}(t)\right] = \sigma^2_{\widehat{PPV}_{cc,r_{D,j},r_{\bar{D},j}}(t)}, \qquad r_i \leq r_j$$

where

$$\sigma^2_{\widehat{PPV}_{cc,r_{D,j},r_{\bar{D},j}}(t)} = \left(\frac{t\,(1-\rho)\,\rho}{\left(ROC(t)\rho + t\,(1-\rho)\right)^2}\right)^2 \sigma^2_{\widehat{ROC}_{r_{D,j},r_{\bar{D},j}}(t)}$$

and $\sigma^2_{\widehat{ROC}_{r_{D,j},r_{\bar{D},j}}(t)}$ *is defined as in Corollary 2.3.*

B. $\left(\widehat{NPV}_{cc,r_{D,1},r_{\bar{D},1}}(t), \widehat{NPV}_{cc,r_{D,2},r_{\bar{D},2}}(t), \ldots, \widehat{NPV}_{cc,r_{D,J},r_{\bar{D},J}}(t)\right)$, *is approximately multivariate normal with,*

$$\widehat{NPV}_{cc,r_{D,i},r_{\bar{D},i}}(t) \sim N\left(NPV(t), \sigma^2_{\widehat{NPV}_{cc,r_{D,i},r_{\bar{D},i}}(t)}\right) \qquad i = 1,2,\ldots,J$$

and

$$Cov\left[\widehat{NPV}_{cc,r_{D,i},r_{\bar{D},i}}(t),\widehat{NPV}_{cc,r_{D,j},r_{\bar{D},j}}(t)\right]=Var\left[\widehat{NPV}_{cc,r_{D,j},r_{\bar{D},j}}(t)\right]=\sigma^2_{\widehat{NPV}_{cc,r_{D,j},r_{\bar{D},j}}(t)},\qquad r_i\leq r_j$$

where

$$\sigma^2_{\widehat{NPV}_{cc,r_{D,j},r_{\bar{D},j}}(t)}=\left(\frac{(1-t)(1-\rho)\rho}{((1-ROC(t))\rho+(1-t)(1-\rho))^2}\right)^2\sigma^2_{\widehat{ROC}_{r_{D,j},r_{\bar{D},j}}(t)}$$

and $\sigma^2_{\widehat{ROC}_{r_{D,j},r_{\bar{D},j}}(t)}$ *is defined as in Corollary 2.3.*

Proof. Immediate from Theorem 3.1. □

Corollary 3.4. *Assume A1 - A4 hold and let* $\frac{f_D(S^{-1}_{\bar{D}}(t))}{f_{\bar{D}}(S^{-1}_{\bar{D}}(t))}$ *be bounded on* $[a,b]$*. For* $t\in(0,1)$*, the empirical estimates of PPV(t) and NPV(t) under case-control sampling are approximately normally distributed with*

$$\widehat{PPV}_{cc,1,1}(t)\sim N\left(PPV(t),\sigma^2_{\widehat{PPV}_{cc,1,1}(t)}\right)$$

and

$$\widehat{NPV}_{cc,1,1}(t)\sim N\left(NPV(t),\sigma^2_{\widehat{NPV}_{cc,1,1}(t)}\right)$$

where $\sigma^2_{\widehat{PPV}_{cc,1,1}(t)}$ *and* $\sigma^2_{\widehat{NPV}_{cc,1,1}(t)}$ *are defined as in Corollary 3.3.*

Proof. Immediate from Corollary 3.3. □

3.2 Under Cohort Sampling

We now turn our attention to estimation of $PPV(t)$ and $NPV(t)$ under cohort sampling. In cohort sampling, disease status is unknown at the time of sampling. Therefore, the number of cases and controls is random at a given time point and we must estimate the prevalence. The sequential empirical estimates of $PPV(t)$ and $NPV(t)$ under cohort sampling can be found by substituting the sequential empirical estimates of $ROC(t)$ and ρ under cohort sampling into (23) and (24). Therefore, the sequential empirical estimates of $PPV(t)$

and $NPV(t)$ under cohort sampling are defined as

$$\widehat{PPV}_{co,r}(t) = \frac{\widehat{ROC}_r(t)\,\hat{\rho}_r}{\widehat{ROC}_r(t)\,\hat{\rho}_r + t\,(1-\hat{\rho}_r)},$$

and

$$\widehat{NPV}_{co,r}(t) = \frac{(1-t)\,(1-\hat{\rho}_r)}{\left(1-\widehat{ROC}_r(t)\right)\hat{\rho}_r + (1-t)\,(1-\hat{\rho}_r)}.$$

Again, we can use the results from Section 2 to develop asymptotic theory for $\widehat{PPV}_{co,r}(t)$ and $\widehat{NPV}_{co,r}(t)$. We begin by showing that $\widehat{PPV}_{co,r}(t)$ and $\widehat{NPV}_{co,r}(t)$ converge to the sum of independent Kiefer Processes.

Theorem 3.5. *Assume A1-A3 hold,* $\rho \in (0,1)$ *and let* $\frac{f_D(S_{\bar{D}}^{-1}(t))}{f_{\bar{D}}(S_{\bar{D}}^{-1}(t))}$ *be bounded on* $[a,b]$.

A. As $n \to \infty$

$$\begin{aligned} n^{-1/2}[nr](\widehat{PPV}_{co,r}(t) - PPV(t)) \to_D & \left(\frac{t\,(1-\rho)\,\rho}{(ROC(t)\rho + t\,(1-\rho))^2}\right)\frac{1}{\sqrt{\rho}}K_3(ROC(t),r) \\ & + \left(\frac{t\,(1-\rho)\,\rho}{(ROC(t)\rho + t\,(1-\rho))^2}\right)\left(\frac{f_D(S_{\bar{D}}^{-1}(t))}{f_{\bar{D}}(S_{\bar{D}}^{-1}(t))}\right)\frac{1}{\sqrt{1-\rho}}K_4(t,r) \\ & + \left(\frac{tROC(t)}{(ROC(t)\rho + t\,(1-\rho))^2}\right)\sqrt{\rho\,(1-\rho)}W(r) \end{aligned}$$

uniformly for $t \in [a,b]$ *and* $r \in [e,1]$ *where* K_3 *and* K_4 *are independent Kiefer Processes and* W *is a Wiener Process independent of* K_3 *and* K_4.

B. As $n \to \infty$

$$\begin{aligned} n^{-1/2}[nr](\widehat{NPV}_{co,r}(t) - NPV(t)) \to_D & \left(\frac{(1-t)\,(1-\rho)\,\rho}{((1-ROC(t))\,\rho + (1-t)\,(1-\rho))^2}\right)\frac{1}{\sqrt{\rho}}K_3(ROC(t),r) \\ & + \left(\frac{(1-t)\,(1-\rho)\,\rho}{((1-ROC(t))\,\rho + (1-t)\,(1-\rho))^2}\right)\left(\frac{f_D(S_{\bar{D}}^{-1}(t))}{f_{\bar{D}}(S_{\bar{D}}^{-1}(t))}\right)\frac{1}{\sqrt{1-\rho}}K_4(t,r) \\ & - \left(\frac{(1-t)\,(1-ROC(t))}{((1-ROC(t))\,\rho + (1-t)\,(1-\rho))^2}\right)\sqrt{\rho\,(1-\rho)}W(r) \end{aligned}$$

uniformly for $t \in [a,b]$ *and* $r \in [e,1]$ *where* K_3 *and* K_4 *are independent Kiefer Processes and* W *is a Wiener Process independent of* K_3 *and* K_4.

Proof. We provide a proof of A but the proof of B is omitted as it is nearly identical. First, note that,

$$\begin{aligned} n^{-1/2}[nr](\widehat{PPV}_{co,r}(t) - PPV(t)) =& n^{-1/2}[nr]\left(\frac{\widehat{ROC}_r(t)\hat{\rho}_r}{\widehat{ROC}_r(t)\hat{\rho}_r + t(1-\hat{\rho}_r)} - \frac{ROC(t)\rho}{ROC(t)\rho + t(1-\rho)}\right) \\ =& n^{-1/2}[nr]\left(\frac{\widehat{ROC}_r(t)\hat{\rho}_r}{\widehat{ROC}_r(t)\hat{\rho}_r + t(1-\hat{\rho}_r)} - \frac{ROC(t)\hat{\rho}_r}{ROC(t)\hat{\rho}_r + t(1-\hat{\rho}_r)}\right) \\ &+ n^{-1/2}[nr]\left(\frac{ROC(t)\hat{\rho}_r}{ROC(t)\hat{\rho}_r + t(1-\hat{\rho}_r)} - \frac{ROC(t)\rho}{ROC(t)\rho + t(1-\rho)}\right). \end{aligned}$$

We begin with the second term, which can be re-written as,

$$\begin{aligned} & n^{-1/2}[nr]\left(\frac{ROC(t)\hat{\rho}_r}{ROC(t)\hat{\rho}_r + t(1-\hat{\rho}_r)} - \frac{ROC(t)\rho}{ROC(t)\rho + t(1-\rho)}\right) \\ &= \frac{\left(\frac{ROC(t)\hat{\rho}_r}{ROC(t)\hat{\rho}_r + t(1-\hat{\rho}_r)} - \frac{ROC(t)\rho}{ROC(t)\rho + t(1-\rho)}\right)}{(\hat{\rho}_r - \rho)} n^{-1/2}[nr](\hat{\rho}_r - \rho). \end{aligned}$$

It is straight-forward to show the $\hat{\rho}_r \rightarrow_{a.s.} \rho$ uniformly for $r \in [e, 1]$,

$$\begin{aligned} \sup_{e \le r \le 1} |\hat{\rho}_r - \rho| =& \frac{n}{[ne]} \sup_{e \le r \le 1} \frac{[ne]}{n} |\hat{\rho}_r - \rho| \\ \le& \frac{n}{[ne]} \sup_{e \le r \le 1} \frac{[nr]}{n} |\hat{\rho}_r - \rho| \\ \rightarrow_{a.s.}& \ 0. \end{aligned}$$

The last step is a result of $\frac{n}{[ne]} \rightarrow \frac{1}{e}$ and the Glivenko-Cantelli Theorems (1.51 and 1.52 in Csörgő and Szyszkowicz (1998)). To see this, note that ρ is equal to the cumulative distribution function for a Bernoulli random variable for any $x \in (0, 1)$. By the Mean Value Theorem, there exists $\tilde{\rho}_r$ between $\hat{\rho}_r$ and ρ such that,

$$\frac{\left(\frac{ROC(t)\hat{\rho}_r}{ROC(t)\hat{\rho}_r + t(1-\hat{\rho}_r)} - \frac{ROC(t)\rho}{ROC(t)\rho + t(1-\rho)}\right)}{(\hat{\rho}_r - \rho)} = \left(\frac{tROC(t)}{(ROC(t)\rho + t(1-\tilde{\rho}_r))^2}\right). \tag{27}$$

The uniform convergence of $\hat{\rho}_r$ to ρ implies that that $\tilde{\rho}_r \rightarrow_{a.s.} \rho$ uniformly for $r \in [e, 1]$. This, along with the uniform continuity of $\left(\frac{tROC(t)}{(ROC(t)\rho + t(1-\rho))^2}\right)$, allows us to conclude that,

$$\sup_{e \le r \le 1} \sup_{a \le t \le b} \left| \left(\frac{tROC(t)}{(ROC(t)\rho + t(1-\tilde{\rho}_r))^2}\right) - \left(\frac{tROC(t)}{(ROC(t)\rho + t(1-\rho))^2}\right) \right| \rightarrow_{a.s.} 0.$$

This result combined with (27) shows that,

$$\frac{\left(\frac{ROC(t)\hat{\rho}_r}{ROC(t)\hat{\rho}_r+t(1-\hat{\rho}_r)}-\frac{ROC(t)\rho}{ROC(t)\rho+t(1-\rho)}\right)}{(\hat{\rho}_r-\rho)}\rightarrow_{a.s.}\left(\frac{tROC(t)}{(ROC(t)\rho+t\,(1-\rho))^2}\right), \tag{28}$$

uniformly for $r\in[e,1]$ and $t\in[a,b]$. Combining (28) with Lemma 2.4 gives us,

$$\begin{aligned}n^{-1/2}[nr]\left(\frac{ROC\,(t)\,\hat{\rho}_r}{ROC\,(t)\,\hat{\rho}_r+t\,(1-\hat{\rho}_r)}-\frac{ROC\,(t)\,\rho}{ROC\,(t)\,\rho+t\,(1-\rho)}\right)&\\ \rightarrow_D\left(\frac{tROC(t)}{(ROC(t)\rho+t\,(1-\rho))^2}\right)\sqrt{\rho\,(1-\rho)}W\,(r)\,,&\end{aligned} \tag{29}$$

uniformly for $r\in[e,1]$ and $t\in[a,b]$.

The first term can be re-written as,

$$\begin{aligned}&n^{-1/2}[nr]\left(\frac{\widehat{ROC}_r(t)\hat{\rho}_r}{\widehat{ROC}_r(t)\hat{\rho}_r+t\,(1-\hat{\rho}_r)}-\frac{ROC\,(t)\,\hat{\rho}_r}{ROC\,(t)\,\hat{\rho}_r+t\,(1-\hat{\rho}_r)}\right)\\ &=\frac{\left(\frac{\widehat{ROC}_r(t)\hat{\rho}_r}{\widehat{ROC}_r(t)\hat{\rho}_r+t(1-\hat{\rho}_r)}-\frac{ROC(t)\hat{\rho}_r}{ROC(t)\hat{\rho}_r+t(1-\hat{\rho}_r)}\right)}{\left(\widehat{ROC}_r(t)-ROC(t)\right)}n^{-1/2}[nr]\left(\widehat{ROC}_r(t)-ROC(t)\right).\end{aligned}$$

By the Mean Value Theorem, there exists $\widetilde{ROC}_r(t)$ between $\widehat{ROC}_r(t)$ and $ROC(t)$ such that,

$$\frac{\left(\frac{\widehat{ROC}_r(t)\hat{\rho}_r}{\widehat{ROC}_r(t)\hat{\rho}_r+t(1-\hat{\rho}_r)}-\frac{ROC(t)\hat{\rho}_r}{ROC(t)\hat{\rho}_r+t(1-\hat{\rho}_r)}\right)}{\left(\widehat{ROC}_r(t)-ROC(t)\right)}=\left(\frac{t\,(1-\hat{\rho}_r)\,\hat{\rho}_r}{\left(\widetilde{ROC}_r(t)\hat{\rho}_r+t\,(1-\hat{\rho}_r)\right)^2}\right).$$

From Lemma 2.5 we know that $\widehat{ROC}_r(t)\rightarrow_{a.s.}ROC(t)$ uniformly for $r\in[e,1]$ and $t\in[a,b]$. This, combined with the uniform convergence of $\hat{\rho}_r$ to ρ and the uniform continuity of $\left(\frac{t(1-\rho)\rho}{(ROC(t)\rho+t(1-\rho))^2}\right)$, gives us,

$$\sup_{e\le r\le 1}\sup_{a\le t\le b}\left|\left(\frac{t\,(1-\hat{\rho}_r)\,\hat{\rho}_r}{\left(\widetilde{ROC}_r(t)\hat{\rho}_r+t\,(1-\hat{\rho}_r)\right)^2}\right)-\left(\frac{t\,(1-\rho)\,\rho}{(ROC(t)\rho+t\,(1-\rho))^2}\right)\right|\rightarrow_{a.s}0,$$

which implies that,

$$\frac{\left(\frac{\widehat{ROC}_{r_D,r_{\bar{D}}}(t)\hat{\rho}_r}{\widehat{ROC}_{r_D,r_{\bar{D}}}(t)\hat{\rho}_r+t(1-\hat{\rho}_r)}-\frac{ROC(t)\hat{\rho}_r}{ROC(t)\hat{\rho}_r+t(1-\hat{\rho}_r)}\right)}{\left(\widehat{ROC}_{r_D,r_{\bar{D}}}(t)-ROC(t)\right)}\rightarrow_{a.s.}\left(\frac{t\,(1-\rho)\,\rho}{(ROC(t)\rho+t\,(1-\rho))^2}\right), \tag{30}$$

uniformly for $r\in[e,1]$ and $t\in[a,b]$. Combining (30) with the results of Lemma 2.6 allows us to conclude that,

$$\frac{\left(\frac{\widehat{ROC}_r(t)\hat{\rho}_r}{\widehat{ROC}_r(t)\hat{\rho}_r+t(1-\hat{\rho}_r)} - \frac{ROC(t)\hat{\rho}_r}{ROC(t)\hat{\rho}_r+t(1-\hat{\rho}_r)}\right)}{\left(\widehat{ROC}_r(t) - ROC(t)\right)} n^{-1/2}[nr]\left(\widehat{ROC}_r(t) - ROC(t)\right)$$

$$\rightarrow_D \left(\frac{t(1-\rho)\rho}{(ROC(t)\rho + t(1-\rho))^2}\right)\frac{1}{\sqrt{\rho}}K_3(ROC(t), r)$$

$$+\left(\frac{t(1-\rho)\rho}{(ROC(t)\rho + t(1-\rho))^2}\right)\left(\frac{f_D(S_{\bar{D}}^{-1}(t))}{f_{\bar{D}}(S_{\bar{D}}^{-1}(t))}\right)\frac{1}{\sqrt{1-\rho}}K_4(t, r). \tag{31}$$

Summing (29) and (31) gives the desired result. □

We are able to derive distribution theory for the fixed-sample estimates of $PPV(t)$ and $NPV(t)$ under cohort sampling as a special case of Theorem 3.5. Corollary 3.6 establishes that the fixed-sample empirical estimates of $PPV(t)$ and $NPV(t)$ converge to the sum of two independent Brownian Bridges.

Corollary 3.6. *Assume A1-A3 hold, $\rho \in (0,1)$ and let $\frac{f_D(S_{\bar{D}}^{-1}(t))}{f_{\bar{D}}(S_{\bar{D}}^{-1}(t))}$ be bounded on $[a,b]$.*

A. As $n \to \infty$

$$n^{1/2}(\widehat{PPV}_{co,1}(t) - PPV(t)) \rightarrow_D \left(\frac{t(1-\rho)\rho}{(ROC(t)\rho + t(1-\rho))^2}\right)\frac{1}{\sqrt{\rho}}B_3(ROC(t))$$

$$+\left(\frac{t(1-\rho)\rho}{(ROC(t)\rho + t(1-\rho))^2}\right)\left(\frac{f_D(S_{\bar{D}}^{-1}(t))}{f_{\bar{D}}(S_{\bar{D}}^{-1}(t))}\right)\frac{1}{\sqrt{1-\rho}}B_4(t)$$

$$+\left(\frac{tROC(t)}{(ROC(t)\rho + t(1-\rho))^2}\right)\sqrt{\rho(1-\rho)}Z$$

uniformly for $t \in [a,b]$ where B_3 and B_4 are independent Brownian Bridges and Z is a standard normal random variable independent of B_3 and B_4.

B. As $n \to \infty$

$$n^{1/2}(\widehat{NPV}_{co,1}(t) - NPV(t)) \rightarrow_D \left(\frac{(1-t)(1-\rho)\rho}{((1-ROC(t))\rho + (1-t)(1-\rho))^2}\right)\frac{1}{\sqrt{\rho}}B_3(ROC(t))$$

$$+\left(\frac{(1-t)(1-\rho)\rho}{((1-ROC(t))\rho + (1-t)(1-\rho))^2}\right)\left(\frac{f_D(S_{\bar{D}}^{-1}(t))}{f_{\bar{D}}(S_{\bar{D}}^{-1}(t))}\right)\frac{1}{\sqrt{1-\rho}}B_4(t)$$

$$-\left(\frac{(1-t)(1-ROC(t))}{((1-ROC(t))\rho + (1-t)(1-\rho))^2}\right)\sqrt{\rho(1-\rho)}Z$$

uniformly for $t \in [a,b]$ where B_3 and B_4 are independent Brownian Bridges and Z is a standard normal random variable independent of B_3 and B_4.

Proof. Immediate from Theorem 3.5. □

The results of Theorem 3.5 and Corollary 3.6 can be used to develop distribution theory for summary measures of the PPV and NPV curves. Corollary 3.7 shows that the sequential emprical estimates of a point on the PPV and NPV curve, $\widehat{PPV}_{co,r}(t)$ and $\widehat{NPV}_{co,r}(t)$, respectively, are asymptotically normal with an independent increments covariance structure, while Corollary 3.8 establishes the asymptotic normality of the fixed-sample empirical estimates of $PPV(t)$ and $NPV(t)$ under cohort sampling.

Corollary 3.7. *Assume A1-A3 hold,* $\rho \in (0,1)$ *and let* $\frac{f_D(S_{\bar{D}}^{-1}(t))}{f_{\bar{D}}(S_{\bar{D}}^{-1}(t))}$ *be bounded on* $[a,b]$*. For* $t \in (0,1)$ *and* J *stopping times,*

A. $\left(\widehat{PPV}_{co,r_1}(t), \widehat{PPV}_{co,r_2}(t), \ldots, \widehat{PPV}_{co,r_J}(t)\right)$*, is approximately multivariate normal with,*

$$\widehat{PPV}_{co,r_i}(t) \sim N\left(PPV(t), \sigma^2_{\widehat{PPV}_{co,r_i}(t)}\right) \qquad i = 1, 2, \ldots, J$$

and

$$Cov\left[\widehat{PPV}_{co,r_i}(t), \widehat{PPV}_{co,r_j}(t)\right] = Var\left[\widehat{PPV}_{co,r_j}(t)\right] = \sigma^2_{\widehat{PPV}_{co,r_j}(t)}, \qquad r_i \le r_j$$

where

$$\sigma^2_{\widehat{PPV}_{co,r_j}(t)} = \left(\frac{t\,(1-\rho)\,\rho}{\left(ROC(t)\rho + t\,(1-\rho)\right)^2}\right)^2 \sigma^2_{\widehat{ROC}_{r_j}(t)} + \left(\frac{tROC(t)}{\left(ROC(t)\rho + t\,(1-\rho)\right)^2}\right)^2 \frac{\rho\,(1-\rho)}{n}$$

and $\sigma^2_{\widehat{ROC}_{r,j}(t)}$ *is defined as in Lemma 2.7.*

B. $\left(\widehat{NPV}_{co,r_1}(t), \widehat{NPV}_{co,r_2}(t), \ldots, \widehat{NPV}_{co,r_J}(t)\right)$*, is approximately multivariate normal with,*

$$\widehat{NPV}_{co,r_i}(t) \sim N\left(NPV(t), \sigma^2_{\widehat{NPV}_{co,r_i}(t)}\right) \qquad i = 1, 2, \ldots, J$$

and

$$Cov\left[\widehat{NPV}_{co,r_i}(t), \widehat{NPV}_{co,r_j}(t)\right] = Var\left[\widehat{NPV}_{co,r_j}(t)\right] = \sigma^2_{\widehat{NPV}_{co,r_j}(t)}, \qquad r_i \le r_j$$

where

$$\sigma^2_{\widehat{NPV}_{co,r_j}(t)} = \left(\frac{(1-t)(1-\rho)\rho}{((1-ROC(t))\rho + (1-t)(1-\rho))^2} \right)^2 \sigma^2_{\widehat{ROC}_{r_j}(t)} + \left(\frac{(1-t)(1-ROC(t))}{((1-ROC(t))\rho + (1-t)(1-\rho))^2} \right)^2 \frac{\rho(1-\rho)}{n}$$

and $\sigma^2_{\widehat{ROC}_{r_j}(t)}$ *is defined as in Lemma 2.7.*

Proof. Immediate from Theorem 3.5. □

Corollary 3.8. *Assume A1-A3 hold,* $\rho \in (0,1)$ *and let* $\frac{f_D(S_{\bar{D}}^{-1}(t))}{f_{\bar{D}}(S_{\bar{D}}^{-1}(t))}$ *be bounded on* $[a,b]$*. For* $t \in (0,1)$*, the empirical estimates of PPV(t) and NPV(t) under cohort sampling are approximately normally distributed with*

$$\widehat{PPV}_{co,1}(t) \sim N\left(PPV(t), \sigma^2_{\widehat{PPV}_{co,1}(t)}\right)$$

and

$$\widehat{NPV}_{co,1}(t) \sim N\left(NPV(t), \sigma^2_{\widehat{NPV}_{co,1}(t)}\right)$$

where $\sigma^2_{\widehat{PPV}_{co,1}(t)}$ *and* $\sigma^2_{\widehat{NPV}_{co,1}(t)}$ *are defined as in Corollary 3.7.*

Proof. Immediate from Corollary 3.7. □

4 PPV and NPV curve indexed by the True Positive Fraction

We next consider the PPV and NPV curves indexed by the true positive fraction, v. In this case, the PPV and NPV curves are defined as $PPV(v) = P[D=1|X > S_D^{-1}(v)]$ and $NPV(v) = P[D=0|X \leq S_D^{-1}(v)]$ for all $v \in (0,1)$. Under this indexing, the PPV and NPV curves can be written as functions of the inverse of the ROC curve

$$\begin{aligned}
PPV(v) =& P[D = 1|X > S_{\bar{D}}^{-1}(v)] \\
=& \frac{P[D = 1, X > S_{\bar{D}}^{-1}(v)]}{P[X > S_{\bar{D}}^{-1}(t)]} \\
=& \frac{P[X > S_{\bar{D}}^{-1}(v)|D = 1]P[D = 1]}{P[X > S_{\bar{D}}^{-1}(v)|D = 1]P[D = 1] + P[X > S_{\bar{D}}^{-1}(v)|D = 0]P[D = 0]} \\
=& \frac{v\rho}{v\rho + ROC^{-1}(v)(1-\rho)}, \qquad (32)
\end{aligned}$$

and

$$NPV(v) = \frac{\left(1 - ROC^{-1}(v)\right)(1-\rho)}{(1-v)\rho + (1 - ROC^{-1}(v))(1-\rho)}. \qquad (33)$$

The sequential empirical estimates of $PPV(v)$ and $NPV(v)$ can be found be plugging the sequential empirical estimate of $ROC^{-1}(v)$ into (32) and (33). It is straight-forward to derive asymptotic theory for $PPV(v)$ and $NPV(v)$ using the results from Section 2.

4.1 Under Case-Control Sampling

We first consider estimation of $PPV(v)$ and $NPV(v)$ under case-control sampling. The sequential empirical estimates of $PPV(v)$ and $NPV(v)$ under case-control sampling can be found by substituting the sequential empirical estimate of $ROC^{-1}(v)$ into (32) and (33) and are therefore defined as

$$\widehat{PPV}_{cc,r_D,r_{\bar{D}}}(v) = \frac{v\rho}{v\rho + \widehat{ROC}_{r_D,r_{\bar{D}}}^{-1}(v)(1-\rho)},$$

and

$$\widehat{NPV}_{cc,r_D,r_{\bar{D}}}(v) = \frac{\left(1 - \widehat{ROC}_{r_D,r_{\bar{D}}}^{-1}(v)\right)(1-\rho)}{(1-v)\rho + \left(1 - \widehat{ROC}_{r_D,r_{\bar{D}}}^{-1}(v)\right)(1-\rho)}.$$

$\widehat{PPV}_{cc,r_D,r_{\bar{D}}}(v)$ and $\widehat{NPV}_{cc,r_D,r_{\bar{D}}}(v)$ are functions of $\widehat{ROC}_{r_D,r_{\bar{D}}}^{-1}(v)$ and we can use the results from Section 2 to derive asymptotic for $\widehat{PPV}_{cc,r_D,r_{\bar{D}}}(v)$ and $\widehat{NPV}_{cc,r_D,r_{\bar{D}}}(v)$. Theorem 4.1 establishes the convergence of $\widehat{PPV}_{cc,r_D,r_{\bar{D}}}(v)$ and $\widehat{NPV}_{cc,r_D,r_{\bar{D}}}(v)$ to the sum of two independent Kiefer Processes.

Theorem 4.1. *Assume A1-A4 hold and let* $\frac{f_{\bar{D}}(S_D^{-1}(v))}{f_D(S_D^{-1}(v))}$ *be bounded on* $[a,b]$.

A. As $n_D \to \infty$ *and* $n_{\bar{D}} \to \infty$

$$n_D^{-1/2}[n_D r_D](\widehat{PPV}_{cc,r_D,r_{\bar{D}}}(v) - PPV(v)) \to_D \left(\frac{v\rho\,(\rho-1)}{\left(v\rho + ROC^{-1}(v)\,(1-\rho)\right)^2}\right)\lambda^{-1/2}\frac{r_D}{r_{\bar{D}}}K_2(ROC^{-1}(v), r_{\bar{D}}) + \left(\frac{v\rho\,(\rho-1)}{\left(v\rho + ROC^{-1}(v)\,(1-\rho)\right)^2}\right)\left(\frac{f_{\bar{D}}(S_D^{-1}(v))}{f_D(S_D^{-1}(v))}\right)K_1(v, r_D)$$

uniformly for $v \in [a,b]$, $r_D \in [c,1]$ *and* $r_{\bar{D}} \in [d,1]$ *where* K_1 *and* K_2 *are independent Kiefer Processes.*

B. As As $n_D \to \infty$ *and* $n_{\bar{D}} \to \infty$

$$n_D^{-1/2}[n_D r_D](\widehat{NPV}_{cc,r_D,r_{\bar{D}}}(v) - NPV(v)) \to_D \left(\frac{\rho\,(1-\rho)\,(v-1)}{\left((1-v)\,\rho + \left(1 - ROC^{-1}(v)\right)(1-\rho)\right)^2}\right)\lambda^{-1/2}\frac{r_D}{r_{\bar{D}}}K_2(ROC^{-1}(v), r_{\bar{D}}) + \left(\frac{\rho\,(1-\rho)\,(v-1)}{\left((1-v)\,\rho + \left(1 - ROC^{-1}(v)\right)(1-\rho)\right)^2}\right)\left(\frac{f_{\bar{D}}(S_D^{-1}(v))}{f_D(S_D^{-1}(v))}\right)K_1(v, r_D)$$

uniformly for $v \in [a,b]$, $r_D \in [c,1]$ *and* $r_{\bar{D}} \in [d,1]$ *where* K_1 *and* K_2 *are independent Kiefer Processes.*

Proof. We only present the proof of part A as the proof of part B is nearly identical. First, note that

$$\begin{aligned}
&n_D^{-1/2}[n_D r_D]\left(\widehat{PPV}_{cc,r_D,r_{\bar{D}}}(v) - PPV(v)\right)) \\
&= n_D^{-1/2}[n_D r_D]\left(\frac{v\rho}{v\rho + \widehat{ROC}^{-1}_{r_D,r_{\bar{D}}}(v)\,(1-\rho)} - \frac{v\rho}{v\rho + ROC^{-1}(v)\,(1-\rho)}\right) \\
&= \frac{\left(\frac{v\rho}{v\rho + \widehat{ROC}^{-1}_{r_D,r_{\bar{D}}}(v)(1-\rho)} - \frac{v\rho}{v\rho + ROC^{-1}(v)(1-\rho)}\right)}{\widehat{ROC}^{-1}_{r_D,r_{\bar{D}}}(v) - ROC^{-1}(v)} n_D^{-1/2}[n_D r_D]\left(\widehat{ROC}^{-1}_{r_D,r_{\bar{D}}}(v) - ROC^{-1}(v)\right).
\end{aligned}$$

We begin by showing that $\widehat{ROC}^{-1}_{r_D,r_{\bar{D}}}(v) \to_{a.s.} ROC^{-1}(v)$ uniformly for $v \in [a,b]$, $r_D \in [c,1]$ and $r_{\bar{D}} \in [c,1]$.

Consider the following inequality,

$$
\begin{aligned}
&\sup_{c\le r_D\le 1}\sup_{d\le r_{\bar D}\le 1}\sup_{a\le v\le b}\left|\widehat{ROC}^{-1}_{r_D,r_{\bar D}}(v)-ROC^{-1}(v)\right|\\
&\quad=\sup_{c\le r_D\le 1}\sup_{d\le r_{\bar D}\le 1}\sup_{a\le v\le b}\left|\hat S_{\bar D,r_{\bar D}}\left(\hat S^{-1}_{D,r_D}(v)\right)-S_{\bar D}\left(S^{-1}_D(v)\right)\right|\\
&\quad\le\sup_{c\le r_D\le 1}\sup_{d\le r_{\bar D}\le 1}\sup_{a\le t\le b}\left|\hat S_{\bar D,r_{\bar D}}\left(\hat S^{-1}_{D,r_D}(v)\right)-S_{\bar D}\left(\hat S^{-1}_{D,r_D}(v)\right)\right|\\
&\qquad+\sup_{c\le r_D\le 1}\sup_{d\le r_{\bar D}\le 1}\sup_{a\le v\le b}\left|S_{\bar D}\left(\hat S^{-1}_{D,r_D}(v)\right)-S_{\bar D}\left(S^{-1}_D(v)\right)\right|\\
&\quad=\frac{n_{\bar D}}{[n_{\bar D}d]}\sup_{c\le r_D\le 1}\sup_{d\le r_{\bar D}\le 1}\sup_{a\le v\le b}\frac{[n_{\bar D}d]}{n_{\bar D}}\left|\hat S_{\bar D,r_{\bar D}}\left(\hat S^{-1}_{D,r_D}(v)\right)-S_{\bar D}\left(\hat S^{-1}_{D,r_D}(v)\right)\right|\\
&\qquad+\frac{n_D}{[n_Dc]}\sup_{d\le r_{\bar D}\le 1}\sup_{a\le v\le b}\frac{[n_Dc]}{n_D}\left|S_{\bar D}\left(S^{-1}_D\left(S_D\left(\hat S^{-1}_{D,r_D}(v)\right)\right)\right)-S_{\bar D}\left(S^{-1}_D(v)\right)\right|\\
&\quad\le\frac{n_{\bar D}}{[n_{\bar D}d]}\sup_{c\le r_D\le 1}\sup_{d\le r_{\bar D}\le 1}\sup_{a\le v\le b}\frac{[n_{\bar D}r_{\bar D}]}{n_{\bar D}}\left|\hat S_{\bar D,r_{\bar D}}\left(\hat S^{-1}_{D,r_D}(v)\right)-S_{\bar D}\left(\hat S^{-1}_{D,r_D}(v)\right)\right|\\
&\qquad+\frac{n_D}{[n_Dc]}\sup_{d\le r_{\bar D}\le 1}\sup_{a\le v\le b}\frac{[n_Dr_D]}{n_D}\left|S_{\bar D}\left(S^{-1}_D\left(S_D\left(\hat S^{-1}_{D,r_D}(v)\right)\right)\right)-S_{\bar D}\left(S^{-1}_D(v)\right)\right|.
\end{aligned}
$$

The Glivenko-Cantelli Theorems (1.51 and 1.52 in Csörgő and Szyszkowicz (1998)), along with the fact that $\frac{n_D}{[n_Dc]}\to\frac{1}{c}$ and $\frac{n_{\bar D}}{[n_{\bar D}d]}\to\frac{1}{d}$ as $n_D\to\infty$ and $n_{\bar D}\to\infty$, respectively, allow us to conclude that

$$\frac{n_{\bar D}}{[n_{\bar D}d]}\sup_{c\le r_D\le 1}\sup_{d\le r_{\bar D}\le 1}\sup_{a\le v\le b}\frac{[n_{\bar D}r_{\bar D}]}{n_{\bar D}}\left|\hat S_{\bar D,r_{\bar D}}\left(\hat S^{-1}_{D,r_D}(v)\right)-S_{\bar D}\left(\hat S^{-1}_{D,r_D}(v)\right)\right|\to_{a.s}0,$$

and

$$\frac{n_D}{[n_Dc]}\sup_{d\le r_{\bar D}\le 1}\sup_{a\le v\le b}\frac{[n_Dr_D]}{n_D}\left|S_{\bar D}\left(S^{-1}_D\left(S_D\left(\hat S^{-1}_{D,r_D}(v)\right)\right)\right)-S_{\bar D}\left(S^{-1}_D(v)\right)\right|\to_{a.s.}0,$$

where the second statement also relies on the uniform continuity of $S_{\bar D}\left(S^{-1}_D(t)\right)$. Combining the two previous results allows us to conclude that

$$\sup_{c\le r_D\le 1}\sup_{d\le r_{\bar D}\le 1}\sup_{a\le v\le b}\left|\widehat{ROC}^{-1}_{r_D,r_{\bar D}}(v)-ROC^{-1}(v)\right|\to_{a.s}0. \tag{34}$$

By the Mean Value Theorem, there exists a $\widetilde{ROC}^{-1}_{r_D,r_{\bar{D}}}(v)$ between $\widehat{ROC}^{-1}_{r_D,r_{\bar{D}}}(v)$ and $ROC^{-1}(v)$ such that

$$\frac{\left(\frac{v\rho}{v\rho+\widehat{ROC}^{-1}_{r_D,r_{\bar{D}}}(v)(1-\rho)} - \frac{v\rho}{v\rho+ROC^{-1}(v)(1-\rho)}\right)}{\widehat{ROC}^{-1}_{r_D,r_{\bar{D}}}(v) - ROC^{-1}(v)} = \frac{v\rho(\rho-1)}{\left(v\rho+\widetilde{ROC}^{-1}_{r_D,r_{\bar{D}}}(v)(1-\rho)\right)^2}.$$

From (34) we know that $\widetilde{ROC}^{-1}_{r_D,r_{\bar{D}}}(v) \to_{a.s.} ROC^{-1}(v)$ and therefore

$$\sup_{c\leq r_D\leq 1}\sup_{d\leq r_{\bar{D}}\leq 1}\sup_{a\leq t\leq b}\left|\frac{v\rho(\rho-1)}{\left(v\rho+\widetilde{ROC}^{-1}_{r_D,r_{\bar{D}}}(v)(1-\rho)\right)^2} - \frac{v\rho(\rho-1)}{\left(v\rho+ROC^{-1}(v)(1-\rho)\right)^2}\right| \to_{a.s.} 0,$$

which allows us to conclude

$$\frac{\left(\frac{v\rho}{v\rho+\widehat{ROC}^{-1}_{r_D,r_{\bar{D}}}(v)(1-\rho)} - \frac{v\rho}{v\rho+ROC^{-1}(v)(1-\rho)}\right)}{\widehat{ROC}^{-1}_{r_D,r_{\bar{D}}}(v) - ROC^{-1}(v)} \to_{a.s.} \frac{v\rho(\rho-1)}{\left(v\rho+ROC^{-1}(v)(1-\rho)\right)^2} \tag{35}$$

uniformly for $v \in [a,b]$, $r_D \in [c,1]$ and $r_{\bar{D}} \in [d,1]$. Combining (35) with the results from Theorem 2.1 gives the desired result. □

Theorem 4.1 is a powerful result that gives insight into the asymptotic behavior of the sequential empirical PPV and NPV curves under case-control sampling. Asymptotic theory is not currently available for the fixed-sample empirical PPV and NPV but can be developed as a special case of the previous result. Corollary 4.2 establishes the convergence of the fixed-sample empirical PPV and NPV curves to the sum of independent Brownian Bridges.

Corollary 4.2. *Assume A1-A4 hold and let* $\frac{f_{\bar{D}}(S_D^{-1}(v))}{f_D(S_D^{-1}(v))}$ *be bounded on* $[a,b]$.

A. As $n_D \to \infty$ *and* $n_{\bar{D}} \to \infty$

$$\begin{aligned} n_D^{1/2}(\widehat{PPV}_{cc,1,1}(v) - PPV(v)) \to_D &\left(\frac{v\rho(\rho-1)}{(v\rho+ROC^{-1}(v)(1-\rho))^2}\right)\lambda^{-1/2}B_2(ROC^{-1}(v)) \\ &+\left(\frac{v\rho(\rho-1)}{(v\rho+ROC^{-1}(v)(1-\rho))^2}\right)\left(\frac{f_{\bar{D}}(S_D^{-1}(v))}{f_D(S_D^{-1}(v))}\right)B_1(v) \end{aligned}$$

uniformly for $v \in [a,b]$ where B_1 and B_2 are independent Brownian Bridges.

B. *As $n_D \to \infty$ and $n_{\bar{D}} \to \infty$*

$$n_D^{1/2}(\widehat{NPV}_{cc,1,1}(v) - NPV(v)) \to_D \left(\frac{\rho\,(1-\rho)\,(v-1)}{((1-v)\,\rho + (1-ROC^{-1}\,(v))\,(1-\rho))^2} \right) \lambda^{-1/2} B_2(ROC^{-1}(v) \\ + \left(\frac{\rho\,(1-\rho)\,(v-1)}{((1-v)\,\rho + (1-ROC^{-1}\,(v))\,(1-\rho))^2} \right) \left(\frac{f_{\bar{D}}(S_D^{-1}(v))}{f_D(S_D^{-1}(v))} \right) B_1(v)$$

uniformly for $v \in [a,b]$ where B_1 and B_2 are independent Brownian Bridges.

Proof. Immediate from Theorem 4.1 and by noting that $K(v,1) =_D B(v)$. □

Theorem 4.1 and Corollary 4.2 allow us to develop distribution theory for summaries of the PPV and NPV curves. The most commonly used summary measures of the PPV and NPV curve are $PPV(v)$, the positive predictive value at a sensitivity equal to v, and $NPV(v)$, the negative predictive value at a sensitivity of v. Theorem 4.3 establishes that the sequential empirical estimates of $PPV(v)$ and $NPV(v)$ are asymptotically normal with an independent increments covariance structure, while Corollary 4.4 establishes the asymptotic normality of the fixed-sample estimate.

Corollary 4.3. *Assume A1-A4 hold and let $\frac{f_{\bar{D}}(S_D^{-1}(v))}{f_D(S_D^{-1}(v))}$ be bounded on $[a,b]$. For $v \in (0,1)$ and J stopping times,*

A. $\left(\widehat{PPV}_{cc,r_{D,1},r_{\bar{D},1}}(v), \widehat{PPV}_{cc,r_{D,2},r_{\bar{D},2}}(v), \ldots, \widehat{PPV}_{cc,r_{D,J},r_{\bar{D},J}}(v)\right)$, *is approximately multivariate normal with,*

$$\widehat{PPV}_{cc,r_{D,i},r_{\bar{D},i}}(v) \sim N\left(PPV(v), \sigma^2_{\widehat{PPV}_{cc,r_{D,i},r_{\bar{D},i}}(v)}\right) \qquad i = 1,2,\ldots,J$$

and

$$Cov\left[\widehat{PPV}_{cc,r_{D,i},r_{\bar{D},i}}(v), \widehat{PPV}_{cc,r_{D,j},r_{\bar{D},j}}(v)\right] = Var\left[\widehat{PPV}_{cc,r_{D,j},r_{\bar{D},j}}(v)\right] = \sigma^2_{\widehat{PPV}_{cc,r_{D,j},r_{\bar{D},j}}(v)}, \qquad r_i \le r_j$$

where

$$\sigma^2_{\widehat{PPV}_{cc,r_{D,j},r_{\bar{D},j}}(v)} = \left(\frac{v\rho\,(\rho-1)}{(v\rho + ROC^{-1}\,(v)\,(1-\rho))^2} \right)^2 \sigma^2_{\widehat{ROC}^{-1}_{r_{D,j},r_{\bar{D},j}}(v)}$$

and $\sigma^2_{\widehat{ROC}_{r_{D,j},r_{\bar{D},j}}(v)}$ is defined as in Corollary 2.3.

B. $\left(\widehat{NPV}_{cc,r_{D,1},r_{\bar{D},1}}(v), \widehat{NPV}_{cc,r_{D,2},r_{\bar{D},2}}(v), \ldots, \widehat{NPV}_{cc,r_{D,J},r_{\bar{D},J}}(v)\right)$, *is approximately multivariate nor-*

mal with,

$$\widehat{NPV}_{cc,r_{D,i},r_{\bar{D},i}}(v) \sim N\left(NPV(v), \sigma^2_{\widehat{NPV}_{cc,r_{D,i},r_{\bar{D},i}}(v)}\right) \qquad i = 1, 2, \ldots, J$$

and

$$Cov\left[\widehat{NPV}_{cc,r_{D,i},r_{\bar{D},i}}(v), \widehat{NPV}_{cc,r_{D,j},r_{\bar{D},j}}(v)\right] = Var\left[\widehat{NPV}_{cc,r_{D,j},r_{\bar{D},j}}(v)\right] = \sigma^2_{\widehat{NPV}_{cc,r_{D,j},r_{\bar{D},j}}(v)}, \qquad r_i \leq r_j$$

where

$$\sigma^2_{\widehat{NPV}_{cc,r_{D,j},r_{\bar{D},j}}(v)} = \left(\frac{\rho\,(1-\rho)\,(v-1)}{\left((1-v)\,\rho + \left(1 - ROC^{-1}\,(v)\right)(1-\rho)\right)^2}\right)^2 \sigma^2_{\widehat{ROC}^{-1}_{r_{D,j},r_{\bar{D},j}}(v)}$$

and $\sigma^2_{\widehat{ROC}_{r_{D,j},r_{\bar{D},j}}(v)}$ *is defined as in Corollary 2.3.*

Proof. Immediate from Theorem 4.1. □

Corollary 4.4. *Assume A1-A4 hold and let* $\frac{f_{\bar{D}}(S_{\bar{D}}^{-1}(v))}{f_D(S_{\bar{D}}^{-1}(v))}$ *be bounded on* $[a, b]$*. For* $v \in (0, 1)$*, the empirical estimates of PPV(v) and NPV(v) under case-control sampling are approximately normally distributed with*

$$\widehat{PPV}_{cc,1,1}(v) \sim N\left(PPV(v), \sigma^2_{\widehat{PPV}_{cc,1,1}(v)}\right)$$

and

$$\widehat{NPV}_{cc,1,1}(v) \sim N\left(NPV(v), \sigma^2_{\widehat{NPV}_{cc,1,1}(v)}\right)$$

where $\sigma^2_{\widehat{PPV}_{cc,1,1}(v)}$ *and* $\sigma^2_{\widehat{NPV}_{cc,1,1}(v)}$ *are defined as in Corollary 4.3.*

Proof. Immediate from Corollary 4.3. □

4.2 Under Cohort Sampling

We next consider estimation of $PPV(v)$ and $NPV(v)$ under cohort sampling. Both ρ and $ROC^{-1}(v)$ must be estimated under cohort sampling. The sequential empirical estimates of $PPV(v)$ and $NPV(v)$ can be found by substituting the sequential empirical estimate of ρ and $ROC^{-1}(v)$ into (32) and (33), respectively, and are defined as

$$\widehat{PPV}_{co,r}(v) = \frac{v\hat{\rho}_r}{v\rho + \widehat{ROC}_r^{-1}(v)\,(1-\hat{\rho}_r)},$$

and

$$\widehat{NPV}_{co,r}(v) = \frac{\left(1 - \widehat{ROC}_r^{-1}(v)\right)(1-\hat{\rho}_r)}{(1-v)\,\hat{\rho}_r + \left(1 - \widehat{ROC}_r^{-1}(v)\right)(1-\hat{\rho}_r)}.$$

Again, the results from Section 2 can be used to develop asymptotic theory for $\widehat{PPV}_{co,r}(v)$ and $\widehat{NPV}_{co,r}(v)$. Theorem 4.5 establishes that $\widehat{PPV}_{co,r}(v)$ and $\widehat{NPV}_{co,r}(v)$ both converge to the sum of two independent Kiefer Processes.

Theorem 4.5. *Assume A1-A3 hold, $\rho \in (0,1)$ and let $\frac{f_{\bar{D}}(S_D^{-1}(v))}{f_D(S_D^{-1}(v))}$ be bounded on $[a,b]$.*

A. As $n \to \infty$

$$\begin{aligned} n^{-1/2}[nr](\widehat{PPV}_{co,r}(v) - PPV(v)) \to_D & \left(\frac{v\rho\,(\rho-1)}{(v\rho + ROC^{-1}(v)\,(1-\rho))^2}\right)\frac{1}{\sqrt{1-\rho}}K_4(ROC^{-1}(v), r) \\ & + \left(\frac{v\rho\,(\rho-1)}{(v\rho + ROC^{-1}(v)\,(1-\rho))^2}\right)\left(\frac{f_{\bar{D}}(S_D^{-1}(v))}{f_D(S_D^{-1}(v))}\right)\frac{1}{\sqrt{\rho}}K_3(v,r) \\ & + \left(\frac{vROC^{-1}(v)}{(v\rho + ROC^{-1}(v)\,(1-\rho))^2}\right)\sqrt{\rho\,(1-\rho)}W(r) \end{aligned}$$

uniformly for $v \in [a,b]$ and $r \in [e,1]$ where K_3 and K_4 are independent Kiefer Processes and W is a Wiener Process independent of K_3 and K_4.

B. As $n \to \infty$

$$\begin{aligned} n^{-1/2}[nr](\widehat{NPV}_{co,r}(v) - NPV(v)) \to_D & \left(\frac{\rho\,(1-\rho)\,(v-1)}{\left((1-v)\,\rho + \left(1 - ROC^{-1}(v)\right)(1-\rho)\right)^2}\right)\frac{1}{\sqrt{1-\rho}}K_4(ROC^{-1}(v), r) \\ & + \left(\frac{\rho\,(1-\rho)\,(v-1)}{\left((1-v)\,\rho + \left(1 - ROC^{-1}(v)\right)(1-\rho)\right)^2}\right)\left(\frac{f_{\bar{D}}(S_D^{-1}(v))}{f_D(S_D^{-1}(v))}\right)\frac{1}{\sqrt{\rho}}K_3(v,r) \\ & - \left(\frac{(1-v)\left(1 - ROC^{-1}(v)\right)}{\left((1-v)\,\rho + \left(1 - ROC^{-1}(v)\right)(1-\rho)\right)^2}\right)\sqrt{\rho\,(1-\rho)}W(r) \end{aligned}$$

uniformly for $v \in [a,b]$ and $r \in [e,1]$ where K_3 and K_4 are independent Kiefer Processes and W is a Wiener Process independent of K_3 and K_4.

Proof. Again, we only present a proof of A because the proof of B is nearly identical. First, note that

$$\begin{aligned} n^{-1/2}[nr](\widehat{PPV}_{co,r}(v) - PPV(v)) = & n^{-1/2}[nr]\left(\frac{v\hat{\rho}_r}{v\hat{\rho}_r + \widehat{ROC}_r^{-1}(v)\,(1-\hat{\rho}_r)} - \frac{v\rho}{v\rho + ROC^{-1}(v)\,(1-\rho)}\right) \\ = & n^{-1/2}[nr]\left(\frac{v\hat{\rho}_r}{v\hat{\rho}_r + \widehat{ROC}_r^{-1}(v)\,(1-\hat{\rho}_r)} - \frac{v\hat{\rho}_r}{v\hat{\rho}_r + ROC^{-1}(v)\,(1-\hat{\rho}_r)}\right) \\ & + n^{-1/2}[nr]\left(\frac{v\hat{\rho}_r}{v\hat{\rho}_r + ROC^{-1}(v)\,(1-\hat{\rho}_r)} - \frac{v\rho}{v\rho + ROC^{-1}(v)\,(1-\rho)}\right) \end{aligned}$$

We begin with the second term, which can be re-written as

$$n^{-1/2}[nr]\left(\frac{v\hat{\rho}_r}{v\hat{\rho}_r + ROC^{-1}(v)\,(1-\hat{\rho}_r)} - \frac{v\rho}{v\rho + ROC^{-1}(v)\,(1-\rho)}\right)$$
$$= \frac{\left(\frac{v\hat{\rho}_r}{v\hat{\rho}_r+ROC^{-1}(v)(1-\hat{\rho}_r)} - \frac{v\rho}{v\rho+ROC^{-1}(v)(1-\rho)}\right)}{(\hat{\rho}_r-\rho)} n^{-1/2}[nr]\,(\hat{\rho}_r-\rho)\,.$$

It is straight-forward to show the $\hat{\rho}_r \rightarrow_{a.s.} \rho$ uniformly for $r \in [e, 1]$,

$$\begin{aligned}\sup_{e\le r\le 1} |\hat{\rho}_r - \rho| &= \frac{n}{[ne]} \sup_{e\le r\le 1} \frac{[ne]}{n} |\hat{\rho}_r - \rho| \\ &\le \frac{n}{[ne]} \sup_{e\le r\le 1} \frac{[nr]}{n} |\hat{\rho}_r - \rho| \\ &\rightarrow_{a.s.} 0.\end{aligned}$$

The last step is a result of $\frac{n}{[ne]} \rightarrow \frac{1}{e}$ and the Glivenko-Cantelli Theorems (1.51 and 1.52 in Csörgő and Szyszkowicz (1998)). To see this, note that ρ is equal to the cumulative distribution function for a Bernoulli random variable for any $x \in (0,1)$. By the Mean Value Theorem, there exists $\tilde{\rho}_r$ between $\hat{\rho}_r$ and ρ such that

$$\frac{\left(\frac{v\hat{\rho}_r}{v\hat{\rho}_r+ROC^{-1}(v)(1-\hat{\rho}_r)} - \frac{v\rho}{v\rho+ROC^{-1}(v)(1-\rho)}\right)}{(\hat{\rho}_r-\rho)} = \frac{vROC^{-1}(v)}{\left(v\tilde{\rho}_r + ROC^{-1}(v)\,(1-\tilde{\rho}_r)\right)^2}. \tag{36}$$

The uniform convergence of $\hat{\rho}_r$ to ρ implies that that $\tilde{\rho}_r \rightarrow_{a.s.} \rho$ uniformly for $r \in [e, 1]$. This, along with the uniform continuity of $\left(\frac{vROC^{-1}(v)}{(v\rho+ROC^{-1}(v)(1-\rho))^2}\right)$, allows us to conclude that

$$\sup_{e\le r\le 1}\ \sup_{a\le v\le b} \left| \frac{vROC^{-1}(v)}{\left(v\tilde{\rho}_r + ROC^{-1}(v)\,(1-\tilde{\rho}_r)\right)^2} - \frac{vROC^{-1}(v)}{\left(v\rho + ROC^{-1}(v)\,(1-\rho)\right)^2} \right| \rightarrow_{a.s.} 0.$$

This result combined with (36) shows that

$$\frac{\left(\frac{v\hat{\rho}_r}{v\hat{\rho}_r+ROC^{-1}(v)(1-\hat{\rho}_r)} - \frac{v\rho}{v\rho+ROC^{-1}(v)(1-\rho)}\right)}{(\hat{\rho}_r-\rho)} \rightarrow_{a.s.} \frac{vROC^{-1}(v)}{\left(v\rho + ROC^{-1}(v)\,(1-\rho)\right)^2}, \tag{37}$$

uniformly for $r \in [e,1]$ and $v \in [a,b]$. Combining (37) and Lemma 2.4 gives us

$$n^{-1/2}[nr]\left(\frac{v\hat{\rho}_r}{v\hat{\rho}_r + ROC^{-1}(v)(1-\hat{\rho}_r)} - \frac{v\rho}{v\rho + ROC^{-1}(v)(1-\rho)}\right) \rightarrow_D \left(\frac{vROC^{-1}(v)}{(v\rho + ROC^{-1}(v)(1-\rho))^2}\right)\sqrt{\rho(1-\rho)}W(r), \quad (38)$$

uniformly for $r \in [e,1]$ and $v \in [a,b]$. The first term can be re-written as

$$n^{-1/2}[nr]\left(\frac{v\hat{\rho}_r}{v\hat{\rho}_r + \widehat{ROC}_r^{-1}(v)(1-\hat{\rho}_r)} - \frac{v\hat{\rho}_r}{v\hat{\rho}_r + ROC^{-1}(v)(1-\hat{\rho}_r)}\right) = \frac{\left(\frac{v\hat{\rho}_r}{v\hat{\rho}_r+\widehat{ROC}_r^{-1}(v)(1-\hat{\rho}_r)} - \frac{v\hat{\rho}_r}{v\hat{\rho}_r+ROC^{-1}(v)(1-\hat{\rho}_r)}\right)}{\left(\widehat{ROC}_r^{-1}(v) - ROC^{-1}(v)\right)} n^{-1/2}[nr]\left(\widehat{ROC}_r^{-1}(v) - ROC^{-1}(v)\right)$$

By the Mean Value Theorem, there exists $\widetilde{ROC}_r^{-1}(v)$ between $\widehat{ROC}_r^{-1}(v)$ and $ROC^{-1}(v)$ such that

$$\frac{\left(\frac{v\hat{\rho}_r}{v\hat{\rho}_r+\widehat{ROC}_r^{-1}(v)(1-\hat{\rho}_r)} - \frac{v\hat{\rho}_r}{v\hat{\rho}_r+ROC^{-1}(v)(1-\hat{\rho}_r)}\right)}{\left(\widehat{ROC}_r^{-1}(v) - ROC^{-1}(v)\right)} = \frac{v\hat{\rho}_r(\hat{\rho}_r - 1)}{\left(v\hat{\rho}_r + \widetilde{ROC}_r^{-1}(v)(1-\hat{\rho}_r)\right)^2}.$$

From Lemma 2.5 we know that $\widehat{ROC}_r^{-1}(v) \rightarrow_{a.s.} ROC^{-1}(v)$ uniformly for $r \in [e,1]$ and $v \in [a,b]$. This, combined with the uniform convergence of $\hat{\rho}_r$ to ρ and the uniform continuity of $\frac{v\rho(\rho-1)}{(v\rho+ROC^{-1}(v)(1-\rho))^2}$ gives us

$$\sup_{e \le r \le 1} \sup_{a \le t \le b} \left| \frac{v\hat{\rho}_r(\hat{\rho}_r - 1)}{\left(v\hat{\rho}_r + \widetilde{ROC}_r^{-1}(v)(1-\hat{\rho}_r)\right)^2} - \frac{v\rho(\rho-1)}{(v\rho + ROC^{-1}(v)(1-\rho))^2} \right| \rightarrow_{a.s} 0,$$

which implies that

$$\frac{\left(\frac{v\hat{\rho}_r}{v\hat{\rho}_r+\widehat{ROC}_r^{-1}(v)(1-\hat{\rho}_r)} - \frac{v\hat{\rho}_r}{v\hat{\rho}_r+ROC^{-1}(v)(1-\hat{\rho}_r)}\right)}{\left(\widehat{ROC}_r^{-1}(v) - ROC^{-1}(v)\right)} \rightarrow_{a.s.} \frac{v\rho(\rho-1)}{(v\rho + ROC^{-1}(v)(1-\rho))^2}, \quad (39)$$

uniformly for $r \in [e,1]$ and $t \in [a,b]$. Combining (39) with the results of Lemma 2.6 allows us to conclude that

$$\frac{\left(\frac{v\hat{\rho}_r}{v\hat{\rho}_r+\widehat{ROC}_r^{-1}(v)(1-\hat{\rho}_r)} - \frac{v\hat{\rho}_r}{v\hat{\rho}_r+ROC^{-1}(v)(1-\hat{\rho}_r)}\right)}{\left(\widehat{ROC}_r^{-1}(v) - ROC^{-1}(v)\right)} n^{-1/2}[nr]\left(\widehat{ROC}_r^{-1}(v) - ROC^{-1}(v)\right)$$
$$\to_D \left(\frac{v\rho(\rho-1)}{\left(v\rho + ROC^{-1}(v)(1-\rho)\right)^2}\right)\frac{1}{\sqrt{1-\rho}}K_4(ROC^{-1}(v), r)$$
$$+ \left(\frac{v\rho(\rho-1)}{\left(v\rho + ROC^{-1}(v)(1-\rho)\right)^2}\right)\left(\frac{f_{\bar{D}}(S_D^{-1}(v))}{f_D(S_D^{-1}(v))}\right)\frac{1}{\sqrt{\rho}}K_3(v, r) \tag{40}$$

Summing (38) and (40) gives the desired result. □

Theorem 4.5 establishes that the sequential empirical estimates of $PPV(v)$ and $NPV(v)$ converge to the sum of two independent Kiefer Processes. We are able to develop an analagous result for the fixed-sample empirical estimates of $PPV(v)$ and $NPV(v)$ as a special case. Corollary 4.6 establishes that the fixed-sample empirical estimates of $PPV(v)$ and $NPV(v)$ converge to the sum of two independent Brownian Bridges under cohort sampling.

Corollary 4.6. *Assume A1-A3 hold, $\rho \in (0,1)$ and let $\frac{f_{\bar{D}}(S_D^{-1}(v))}{f_D(S_D^{-1}(v))}$ be bounded on $[a,b]$.*

A. As $n \to \infty$

$$n^{1/2}(\widehat{PPV}_{co,1}(v) - PPV(v)) \to_D \left(\frac{v\rho(\rho-1)}{(v\rho + ROC^{-1}(v)(1-\rho))^2}\right)\frac{1}{\sqrt{1-\rho}}B_4(ROC^{-1}(v))$$
$$+ \left(\frac{v\rho(\rho-1)}{(v\rho + ROC^{-1}(v)(1-\rho))^2}\right)\left(\frac{f_{\bar{D}}(S_D^{-1}(v))}{f_D(S_D^{-1}(v))}\right)\frac{1}{\sqrt{\rho}}B_3(v)$$
$$+ \left(\frac{vROC^{-1}(v)}{(v\rho + ROC^{-1}(v)(1-\rho))^2}\right)\sqrt{\rho(1-\rho)}Z$$

uniformly for $v \in [a,b]$ where B_3 and B_4 are independent Brownian Bridges and Z is a standard normal random variable independent of B_3 and B_4.

B. As $n \to \infty$

$$n^{1/2}(\widehat{NPV}_{co,1}(v) - NPV(v)) \to_D \sqrt{\frac{1}{1-\rho}}\left(\frac{\rho(1-\rho)(v-1)}{((1-v)\rho + (1-ROC^{-1}(v))(1-\rho))^2}\right)B_4(ROC^{-1}(v))$$
$$+ \sqrt{\frac{1}{\rho}}\left(\frac{\rho(1-\rho)(v-1)}{((1-v)\rho + (1-ROC^{-1}(v))(1-\rho))^2}\right)\left(\frac{f_{\bar{D}}(S_D^{-1}(v))}{f_D(S_D^{-1}(v))}\right)B_3(v)$$
$$- \left(\frac{(1-v)(1-ROC^{-1}(v))}{((1-v)\rho + (1-ROC^{-1}(v))(1-\rho))^2}\right)\sqrt{\rho(1-\rho)}Z$$

uniformly for $v \in [a,b]$ where B_3 and B_4 are independent Brownian Bridges and Z is a standard normal random variable independent of B_3 and B_4.

Proof. Immediate from Theorem 4.5 and by noting that $K(v,1) =_D B(v)$. □

Again, we are able to develop distribution theory for summary measures of $PPV(v)$ and $NPV(v)$ using the results of Theorem 4.5 and Corollary 4.6. Corollary 4.7 establishes that the sequential empirical estimate of a point on the PPV or NPV curve is asymptotically normal with an independent increments covariance structure, while Corollary 4.8 establishes the asymptotic normality of the fixed-sample empirical estimates of $PPV(v)$ and $NPV(v)$.

Corollary 4.7. *Assume A1-A3 hold, $\rho \in (0,1)$ and let $\frac{f_{\bar{D}}(S_D^{-1}(v))}{f_D(S_D^{-1}(v))}$ be bounded on $[a,b]$. For $v \in (0,1)$ and J stopping times,*

A. $\left(\widehat{PPV}_{co,r_1}(v), \widehat{PPV}_{co,r_2}(v), \ldots, \widehat{PPV}_{co,r_J}(v)\right)$, *is approximately multivariate normal with,*

$$\widehat{PPV}_{co,r_i}(v) \sim N\left(PPV(v), \sigma^2_{\widehat{PPV}_{co,r_i}(v)}\right) \qquad i = 1,2,\ldots,J$$

and

$$Cov\left[\widehat{PPV}_{co,r_i}(v), \widehat{PPV}_{co,r_j}(v)\right] = Var\left[\widehat{PPV}_{co,r_j}(v)\right] = \sigma^2_{\widehat{PPV}_{co,r_j}(v)}, \qquad r_i \leq r_j$$

where

$$\sigma^2_{\widehat{PPV}_{co,r_j}(v)} = \left(\frac{v\rho\,(\rho-1)}{\left(v\rho + ROC^{-1}(v)\,(1-\rho)\right)^2}\right)^2 \sigma^2_{\widehat{ROC}^{-1}_{r_j}(v)} + \left(\frac{vROC^{-1}(v)}{\left(v\rho + ROC^{-1}(v)\,(1-\rho)\right)^2}\right)^2 \frac{\rho\,(1-\rho)}{n}$$

and $\sigma^2_{\widehat{ROC}_{r_j}(v)}$ is defined as in Lemma 2.7.

B. $\left(\widehat{NPV}_{co,r_1}(v), \widehat{NPV}_{co,r_2}(v), \ldots, \widehat{NPV}_{co,r_J}(v)\right)$, *is approximately multivariate normal with,*

$$\widehat{NPV}_{co,r_i}(v) \sim N\left(NPV(v), \sigma^2_{\widehat{NPV}_{co,r_i}(v)}\right) \qquad i = 1,2,\ldots,J$$

and

$$Cov\left[\widehat{NPV}_{co,r_i}(v), \widehat{NPV}_{co,r_j}(v)\right] = Var\left[\widehat{NPV}_{co,r_j}(v)\right] = \sigma^2_{\widehat{NPV}_{co,r_j}(v)}, \qquad r_i \leq r_j$$

where

$$\sigma^2_{\widehat{NPV}_{co,r_j}(v)} = \left(\frac{\rho(1-\rho)(v-1)}{\left((1-v)\rho + (1-ROC^{-1}(v))(1-\rho)\right)^2}\right)^2 \sigma^2_{\widehat{ROC}^{-1}_{r_j}(v)} + \left(\frac{(1-v)\left(1-ROC^{-1}(v)\right)}{\left((1-v)\rho + (1-ROC^{-1}(v))(1-\rho)\right)^2}\right)^2 \frac{\rho(1-\rho)}{n}$$

and $\sigma^2_{\widehat{ROC}_{r_j}(v)}$ *is defined as in Lemma 2.7.*

Proof. Immediate from Theorem 4.5. □

Corollary 4.8. *Assume A1-A3 hold,* $\rho \in (0,1)$ *and let* $\frac{f_{\bar{D}}(S_{\bar{D}}^{-1}(v))}{f_D(S_{\bar{D}}^{-1}(v))}$ *be bounded on* $[a,b]$*. For* $v \in (0,1)$*, the empirical estimates of PPV(v) and NPV(v) under cohort sampling are approximately normally distributed with*

$$\widehat{PPV}_{co,1}(v) \sim N\left(PPV(v), \sigma^2_{\widehat{PPV}_{co,1}(v)}\right)$$

and

$$\widehat{NPV}_{co,1}(v) \sim N\left(NPV(v), \sigma^2_{\widehat{NPV}_{co,1}(v)}\right)$$

where $\sigma^2_{\widehat{PPV}_{co,1}(v)}$ *and* $\sigma^2_{\widehat{NPV}_{co,1}(v)}$ *are defined as in Corollary 4.7.*

Proof. Immediate from Corollary 4.7. □

5 PPV and NPV curve indexed by the Percentile Value

Finally, we consider the PPV and NPV curves indexed by the proportion of the population that are classified as negative, u, and positive, $1-u$. In this case, the PPV and NPV curves are defined as $PPV(u) = P[D = 1|X > F^{-1}(u)]$ and $NPV(u) = P[D = 0|X \leq F^{-1}(u)]$ for all $u \in (0,1)$. Under this indexing, the PPV curve can be written as

$$
\begin{aligned}
PPV(u) &= P\left[D=1|X>F^{-1}(u)\right] \\
&= \frac{P\left[D=1, X>F^{-1}(u)\right]}{P\left[X>F^{-1}(u)\right]} \\
&= \frac{P\left[X>F^{-1}(u)|D=1\right] * P\left[D=1\right]}{1-F\left(F^{-1}(u)\right)} \\
&= \frac{S_D\left(F^{-1}(u)\right)\rho}{1-u}, \qquad (41)
\end{aligned}
$$

and

$$NPV(u) = \frac{F_{\bar{D}}\left(F^{-1}(u)\right)(1-\rho)}{u}.$$

It should also be noted that the NPV curve can be expressed as a function of the PPV curve

$$NPV(u) = \frac{u-\rho}{u} + \frac{1-u}{u} PPV(u), \qquad (42)$$

and, therefore, it suffices to study the PPV curve when considering estimation of the PPV and NPV curves.

5.1 Case-Control Sampling

In this section, we consider the sequential empirical estimates of $PPV(u)$ and $NPV(u)$ under case-control sampling. The sequential empirical estimate of $PPV(u)$ under case-control sampling can be found by substituting the sequential empirical estimates of $S_D(x)$ and $F(x)$, along with the known value of ρ, into (41),

$$\widehat{PPV}_{cc,r_D,r_{\bar{D}}}(u) = \frac{\hat{S}_{D,r_D}\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)\rho}{1-u}. \qquad (43)$$

$NPV(u)$ can be expressed as a function of $PPV(u)$ and, therefore, the sequential empirical estimate of $NPV(u)$ is found by substituting the sequential empirical estimate of $PPV(u)$ into (42),

$$\widehat{NPV}_{cc,r_D,r_{\bar{D}}}(u) = \frac{u-\rho}{u} + \frac{1-u}{u}\widehat{PPV}_{cc,r_D,r_{\bar{D}}}(u). \qquad (44)$$

We begin by showing that $\widehat{PPV}_{cc,r_D,r_{\bar{D}}}(u)$ converges to the sum of two independent Kiefer process in Theorem 5.1. The proof of Theorem 5.1 follows the proofs found in Pyke and Shorack (1968).

Theorem 5.1. *Assume A1 - A4 hold and let* $\frac{f_D(F^{-1}(u))}{f(F^{-1}(u))}$ *be bounded on* $[a,b]$*. As* $n_D \to \infty$ *and* $n_{\bar{D}} \to \infty$

$$
\begin{aligned}
n_D^{-1/2}\left[n_D r_D\right]\left(\widehat{PPV}_{cc,r_D,r_{\bar{D}}}(u) - PPV(u)\right) \to_D & -\frac{\rho(1-\rho)}{1-u}\frac{f_{\bar{D}}\left(F^{-1}(u)\right)}{f\left(F^{-1}(u)\right)} K_1(F_D(F^{-1}(u)), r_D) \\
& + \frac{\rho(1-\rho)}{1-u}\frac{f_D\left(F^{-1}(u)\right)}{f\left(F^{-1}(u)\right)}\sqrt{\lambda}\frac{r_D}{r_{\bar{D}}} K_2(F_{\bar{D}}(F^{-1}(u)), r_{\bar{D}})
\end{aligned}
$$

uniformly for $u \in [a,b]$*,* $r_D \in [c,1]$ *and* $r_{\bar{D}} \in [d,1]$ *where* K_1 *and* K_2 *are independent Kiefer Processes.*

Proof. First, note that,

$$
\begin{aligned}
n_D^{-1/2}\left[n_D r_D\right]\left(\hat{S}_{D,r_D}\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right) - S_D\left(F^{-1}(u)\right)\right) = & n_D^{-1/2}\left[n_D r_D\right]\left(F_D\left(F^{-1}(u)\right) - \hat{F}_{D,r_D}\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)\right) \\
= & n_D^{-1/2}\left[n_D r_D\right]\left(F_D\left(F^{-1}(u)\right) - F_D\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)\right) \\
& + n_D^{-1/2}\left[n_D r_D\right]\left(F_D\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right) - \hat{F}_{D,r_D}\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)\right).
\end{aligned}
$$

The first term can be rewritten as,

$$
\begin{aligned}
& n_D^{-1/2}\left[n_D r_D\right]\left(F_D\left(F^{-1}(u)\right) - F_D\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)\right) \\
= & n_D^{-1/2}\left[n_D r_D\right]\frac{F_D\left(F^{-1}(u)\right) - F_D\left(F^{-1}\left(F\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)\right)\right)}{u - F\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)}\left(u - F\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)\right) \\
= & n_D^{-1/2}\left[n_D r_D\right]\frac{F_D\left(F^{-1}\left(F\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)\right)\right) - F_D\left(F^{-1}(u)\right)}{F\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right) - u}\left(u - \hat{F}_{r_D,r_{\bar{D}}}\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)\right) \\
& + n_D^{-1/2}\left[n_D r_D\right]\frac{F_D\left(F^{-1}\left(F\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)\right)\right) - F_D\left(F^{-1}(u)\right)}{F\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right) - u}\left(\hat{F}_{r_D,r_{\bar{D}}}\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right) - F\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)\right) \\
= & \frac{F_D\left(F^{-1}\left(F\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)\right)\right) - F_D\left(F^{-1}(u)\right)}{F\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right) - u} n_D^{-1/2}\left[n_D r_D\right]\left(u - \hat{F}_{r_D,r_{\bar{D}}}\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)\right) \\
& + \frac{F_D\left(F^{-1}\left(F\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)\right)\right) - F_D\left(F^{-1}(u)\right)}{F\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right) - u}\rho n_D^{-1/2}\left[n_D r_D\right]\left(\hat{F}_{D,r_D}\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right) - F_D\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)\right) \\
& + \frac{n_D^{-1/2}\left[n_D r_D\right]}{n_{\bar{D}}^{-1/2}\left[n_{\bar{D}} r_{\bar{D}}\right]}\frac{F_D\left(F^{-1}\left(F\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)\right)\right) - F_D\left(F^{-1}(u)\right)}{F\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right) - u}(1-\rho)\, n_{\bar{D}}^{-1/2}\left[n_{\bar{D}} r_{\bar{D}}\right]\left(\hat{F}_{\bar{D},r_{\bar{D}}}\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right) - F_{\bar{D}}\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)\right)
\end{aligned}
$$

We begin by showing that $F\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)$ converges to u uniformly,

$$\sup_{c\le r_D\le 1}\sup_{d\le r_{\bar{D}}\le 1}\sup_{a\le u\le b}\left|F\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)-u\right|$$
$$\le \sup_{c\le r_D\le 1}\sup_{d\le r_{\bar{D}}\le 1}\sup_{a\le u\le b}\left|F\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)-\hat{F}_{r_D,r_{\bar{D}}}\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)\right|$$
$$+\sup_{c\le r_D\le 1}\sup_{d\le r_{\bar{D}}\le 1}\sup_{a\le u\le b}\left|\hat{F}_{r_D,r_{\bar{D}}}\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)-u\right|.$$

We note that,

$$\sup_{c\le r_D\le 1}\sup_{d\le r_{\bar{D}}\le 1}\sup_{a\le u\le b}\left|F\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)-\hat{F}_{r_D,r_{\bar{D}}}\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)\right|$$
$$\le \sup_{c\le r_D\le 1}\sup_{d\le r_{\bar{D}}\le 1}\sup_{a\le u\le b}\left|F_D\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)-\hat{F}_{D,r_D}\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)\right|$$
$$+\sup_{c\le r_D\le 1}\sup_{d\le r_{\bar{D}}\le 1}\sup_{a\le u\le b}\left|F_{\bar{D}}\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)-\hat{F}_{\bar{D},r_{\bar{D}}}\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)\right|$$
$$=\frac{n_D}{[n_Dc]}\sup_{c\le r_D\le 1}\sup_{d\le r_{\bar{D}}\le 1}\sup_{a\le u\le b}\frac{[n_Dc]}{n_D}\left|F_D\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)-\hat{F}_{D,r_D}\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)\right|$$
$$+\frac{n_{\bar{D}}}{[n_{\bar{D}}d]}\sup_{c\le r_D\le 1}\sup_{d\le r_{\bar{D}}\le 1}\sup_{a\le u\le b}\frac{[n_{\bar{D}}d]}{n_{\bar{D}}}\left|F_{\bar{D}}\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)-\hat{F}_{\bar{D},r_{\bar{D}}}\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)\right|$$
$$\le\frac{n_D}{[n_Dc]}\sup_{c\le r_D\le 1}\sup_{d\le r_{\bar{D}}\le 1}\sup_{a\le u\le b}\frac{[n_Dr_D]}{n_D}\left|F_D\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)-\hat{F}_{D,r_D}\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)\right|$$
$$+\frac{n_{\bar{D}}}{[n_{\bar{D}}d]}\sup_{c\le r_D\le 1}\sup_{d\le r_{\bar{D}}\le 1}\sup_{a\le u\le b}\frac{[n_{\bar{D}}r_{\bar{D}}]}{n_{\bar{D}}}\left|F_{\bar{D}}\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)-\hat{F}_{\bar{D},r_{\bar{D}}}\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)\right|$$
$$\to_{a.s.}0,$$

by the Glivenko-Cantelli Theorems (1.51 and 1.52 in Csörgő and Szyszkowicz (1998)), along with the fact that $\frac{n_D}{[n_Dc]}\to\frac{1}{c}$ and $\frac{n_{\bar{D}}}{[n_{\bar{D}}d]}\to\frac{1}{d}$. For all $r_D, r_{\bar{D}}\in(0,1]\times(0,1]$,

$$\sup_{a\le u\le b}\left|u-\hat{F}_{r_D,r_{\bar{D}}}\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)\right|\le_{a.s.}\left(\frac{\rho}{[r_Dn_D]}\bigvee\frac{1-\rho}{[n_{\bar{D}}r_{\bar{D}}]}\right).$$

Therefore,

$$\sup_{c\le r_D\le 1}\sup_{d\le r_{\bar{D}}\le 1}\sup_{a\le u\le b}\left|u-\hat{F}_{r_D,r_{\bar{D}}}\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)\right|\le_{a.s.}\left(\frac{\rho}{[n_Dc]}\bigvee\frac{1-\rho}{[n_{\bar{D}}d]}\right)\to 0,$$

which implies that,

$$\sup_{c<r_D\le 1}\sup_{d<r_{\bar{D}}\le 1}\sup_{a\le u\le b}\left|F\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)-u\right|\to_{a.s.}0. \tag{45}$$

We note that (45) also implies that $F_D\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)$ and $F_{\bar{D}}\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)$ converge uniformly to $F_D\left(F^{-1}(u)\right)$ and $F_{\bar{D}}\left(F^{-1}(u)\right)$, respectively, which can be seen by noting that the difference between $F_D\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)$ and $F_D\left(F^{-1}(u)\right)$ will always have the same sign as the difference between $F_{\bar{D}}\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)$ and $F_{\bar{D}}\left(F^{-1}(u)\right)$.

By the mean value theorem, there exists $F\left(\tilde{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)$ between u and $F\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)$, such that,

$$\frac{F_D\left(F^{-1}\left(F\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)\right)\right)-F_D\left(F^{-1}(u)\right)}{F\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)-u}=\frac{f_D\left(F^{-1}\left(F\left(\tilde{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)\right)\right)}{f\left(F^{-1}\left(F\left(\tilde{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)\right)\right)}.$$

The uniform continuity of $\frac{f_D\left(F^{-1}(u)\right)}{f\left(F^{-1}(u)\right)}$, combined with the fact that $F\left(\tilde{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)\to_{a.s.} u$ uniformly, allows us to conclude,

$$\sup_{c<r_D\leq 1}\ \sup_{d<r_{\bar{D}}\leq 1}\ \sup_{a\leq u\leq b}\left|\frac{f_D\left(F^{-1}\left(F\left(\tilde{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)\right)\right)}{f\left(F^{-1}\left(F\left(\tilde{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)\right)\right)}-\frac{f_D\left(F^{-1}(u)\right)}{f\left(F^{-1}(u)\right)}\right|\to_{a.s.} 0. \tag{46}$$

For all $r_D, r_{\bar{D}}\in(0,1]\times(0,1]$,

$$\sup_{a\leq u\leq b} n_D^{-1/2}\left[n_D r_D\right]\left|u-\hat{F}_{r_D,r_{\bar{D}}}\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)\right|\leq_{a.s.}\left(\frac{\rho}{n_D^{-1/2}}\bigvee\frac{\left[n_D r_D\right]}{\left[n_{\bar{D}} r_{\bar{D}}\right]}\frac{1-\rho}{n_D^{-1/2}}\right).$$

Therefore, as $n_D\to\infty$ and $n_{\bar{D}}\to\infty$,

$$\sup_{0<r_D\leq 1}\ \sup_{0<r_{\bar{D}}\leq 1}\ \sup_{a\leq u\leq b} n_D^{-1/2}\left[n_D r_D\right]\left|u-\hat{F}_{r_D,r_{\bar{D}}}\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)\right|\to_{a.s.} 0.$$

Combining this result with (46) allows us to conclude that,

$$\frac{F_D\left(F^{-1}\left(F\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)\right)\right)-F_D\left(F^{-1}(u)\right)}{F\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)-u}n_D^{-1/2}\left[n_D r_D\right]\left(u-\hat{F}_{r_D,r_{\bar{D}}}\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)\right)\to_{a.s.} 0.$$

Corollary 1.A in Csörgő and Szyszkowicz (1998), (46) and the uniform continuity of the Kiefer process allow us to conclude,

$$\frac{F_D\left(F^{-1}\left(F\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)\right)\right)-F_D\left(F^{-1}(u)\right)}{F\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)-u}\rho n_D^{-1/2}\left[n_D r_D\right]\left(\hat{F}_{D,r_D}\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)-F_D\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)\right)$$
$$\to_D \frac{f_D\left(F^{-1}(u)\right)}{f\left(F^{-1}(u)\right)}\rho K_1\left(F_D\left(F^{-1}(u)\right),r_D\right), \tag{47}$$

and,

$$\frac{n_D^{-1/2}\left[n_D r_D\right]}{n_{\bar{D}}^{-1/2}\left[n_{\bar{D}} r_{\bar{D}}\right]}\frac{F_D\left(F^{-1}\left(F\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)\right)\right)-F_D\left(F^{-1}(u)\right)}{F\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)-u}(1-\rho)\,n_{\bar{D}}^{-1/2}\left[n_{\bar{D}} r_{\bar{D}}\right]\left(\hat{F}_{\bar{D},r_{\bar{D}}}\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)-F_{\bar{D}}\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)\right)$$
$$\to_D \sqrt{\lambda}\frac{r_D}{r_{\bar{D}}}\frac{f_D\left(F^{-1}(u)\right)}{f\left(F^{-1}(u)\right)}(1-\rho)\,K_2\left(F_{\bar{D}}\left(F^{-1}(u)\right),r_D\right). \tag{48}$$

The second term converges in distribution to a Kiefer process,

$$n_D^{-1/2}\left[n_D r_D\right]\left(F_D\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)-\hat{F}_{D,r_D}\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)\right)=-\,n_D^{-1/2}\left[n_D r_D\right]\left(\hat{F}_{D,r_D}\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)-F_D\left(\hat{F}^{-1}_{r_D,r_{\bar{D}}}(u)\right)\right)$$
$$\to_D -K_1\left(F_D\left(F^{-1}(u)\right),r_D\right), \tag{49}$$

by Corollary 1.A in Csörgő and Szyszkowicz (1998). Summing (47), (48) and (49) gives the desired result. □

Theorem 5.1 establishes the convergence of the sequential empirical PPV curve to the sum of two independent Kiefer Processes under case-control sampling. From this result we are able to derive distribution theory for the fixed-sample empirical estimate of $PPV(u)$, as well as the sequential and fixed-sample empirical estimates of $NPV(u)$. Corollary 5.2 establishes the convergence in distribution for the fixed-sample empirical estimate of $PPV(u)$, while Corollary 5.3 provide results analagous to Theorem 5.1 and Corollary 5.2 for the NPV curve.

Corollary 5.2. *Assume A1 - A4 hold and let* $\frac{f_D\left(F^{-1}(u)\right)}{f(F^{-1}(u))}$ *be bounded on* $[a,b]$. *As* $n_D\to\infty$ *and* $n_{\bar{D}}\to\infty$

$$n_D^{1/2}\left(\widehat{PPV}_{cc,1,1}(u)-PPV(u)\right)\to_D -\frac{\rho(1-\rho)}{1-u}\frac{f_{\bar{D}}\left(F^{-1}(u)\right)}{f\left(F^{-1}(u)\right)}B_1(F_D(F^{-1}(u)))$$
$$+\frac{\rho(1-\rho)}{1-u}\frac{f_D\left(F^{-1}(u)\right)}{f\left(F^{-1}(u)\right)}\sqrt{\lambda}\frac{r_D}{r_{\bar{D}}}B_2(F_{\bar{D}}(F^{-1}(u)))$$

uniformly for $u\in[a,b]$ *where* B_1 *and* B_2 *are independent Brownian Bridges.*

Proof. Immediate from Theorem 5.1 and by noting that $K(t,1)=_D B(t)$. □

Corollary 5.3. *Assume A1 - A4 hold and let* $\frac{f_D(F^{-1}(u))}{f(F^{-1}(u))}$ *be bounded on* $[a,b]$*. As* $n_D \to \infty$ *and* $n_{\bar{D}} \to \infty$

$$n_D^{-1/2}\,[n_D r_D]\left(\widehat{NPV}_{cc,r_D,r_{\bar{D}}}(u) - NPV(u)\right) \to_D -\frac{\rho(1-\rho)}{u}\frac{f_{\bar{D}}(F^{-1}(u))}{f(F^{-1}(u))}K_1(F_D(F^{-1}(u)), r_D)$$
$$+\frac{\rho(1-\rho)}{u}\frac{f_D(F^{-1}(u))}{f(F^{-1}(u))}\sqrt{\lambda}\frac{r_D}{r_{\bar{D}}}K_2(F_{\bar{D}}(F^{-1}(u)), r_{\bar{D}})$$

uniformly for $u \in [a,b]$*,* $r_D \in [c,1]$ *and* $r_{\bar{D}} \in [d,1]$ *where* K_1 *and* K_2 *are independent Kiefer Processes and*

$$n_D^{1/2}\left(\widehat{NPV}_{cc,1,1}(u) - NPV(u)\right) \to_D -\frac{\rho(1-\rho)}{u}\frac{f_{\bar{D}}(F^{-1}(u))}{f(F^{-1}(u))}B_1(F_D(F^{-1}(u)))$$
$$+\frac{\rho(1-\rho)}{u}\frac{f_D(F^{-1}(u))}{f(F^{-1}(u))}\sqrt{\lambda}B_2(F_{\bar{D}}(F^{-1}(u)))$$

uniformly for $u \in [a,b]$ *where* B_1 *and* B_2 *are independent Brownian Bridges.*

Proof. Immediate from Theorem 5.1, Corollary 5.2 and (42). □

Theorem 5.1, Corollary 5.2 and Corollary 5.3 allow us to develop distribution theory for summaries of the PPV and NPV curves. The most common summaries of the PPV and NPV curves are $PPV(u)$ and $NPV(u)$, respectively. $PPV(u)$ and $NPV(u)$ are the positive and negative predictive values when biomarkers values at the *uth* percentile or above are considered positive. The following corollary provides a normal approximation for the sequential empirical estimates of $PPV(u)$ and $NPV(u)$.

Corollary 5.4. *Assume A1 - A4 hold and let* $\frac{f_D(F^{-1}(u))}{f(F^{-1}(u))}$ *be bounded on* $[a,b]$*. For* $u \in (0,1)$ *and J stopping times,*

A. $\left(\widehat{PPV}_{cc,r_{D,1},r_{\bar{D},1}}(u), \widehat{PPV}_{cc,r_{D,2},r_{\bar{D},2}}(u), \ldots, \widehat{PPV}_{cc,r_{D,J},r_{\bar{D},J}}(u)\right)$*, is approximately multivariate normal with,*

$$\widehat{PPV}_{cc,r_{D,i},r_{\bar{D},i}}(u) \sim N\left(PPV(u), \sigma^2_{\widehat{PPV}_{cc,r_{D,i},r_{\bar{D},i}}(u)}\right) \qquad i = 1,2,\ldots,J$$

and

$$Cov\left[\widehat{PPV}_{cc,r_{D,i},r_{\bar{D},i}}(u),\ \widehat{PPV}_{cc,r_{D,j},r_{\bar{D},j}}(u)\right] = Var\left[\widehat{PPV}_{cc,r_{D,j},r_{\bar{D},j}}(u)\right] = \sigma^2_{\widehat{PPV}_{cc,r_{D,j},r_{\bar{D},j}}(u)}, \qquad r_i \le r_j$$

where

$$\sigma^2_{\widehat{PPV}_{cc,r_{D,j},r_{\bar{D},j}}(u)} = \frac{\left(\frac{f_{\bar{D}}\left(F^{-1}(u)\right)}{f(F^{-1}(u))}(1-\rho)\right)^2 PPV(u)\left(\frac{\rho}{1-u} - PPV(u)\right)}{n_D r_{D,j}} + \frac{\left(\frac{f_D\left(F^{-1}(u)\right)}{f(F^{-1}(u))}\rho\right)^2 (1-PPV(u))\left(\frac{u-\rho}{1-u} + PPV(u)\right)}{n_{\bar{D}} r_{\bar{D},j}}.$$

B. $\left(\widehat{NPV}_{cc,r_{D,1},r_{\bar{D},1}}(u), \widehat{NPV}_{cc,r_{D,2},r_{\bar{D},2}}(u), \ldots, \widehat{NPV}_{cc,r_{D,J},r_{\bar{D},J}}(u)\right)$, *is approximately multivariate normal with,*

$$\widehat{NPV}_{cc,r_{D,i},r_{\bar{D},i}}(u) \sim N\left(NPV(u), \sigma^2_{\widehat{NPV}_{cc,r_{D,i},r_{\bar{D},i}}(u)}\right) \qquad i = 1, 2, \ldots, J$$

and

$$Cov\left[\widehat{NPV}_{cc,r_{D,i},r_{\bar{D},i}}(u),\ \widehat{NPV}_{cc,r_{D,j},r_{\bar{D},j}}(u)\right] = Var\left[\widehat{NPV}_{cc,r_{D,j},r_{\bar{D},j}}(u)\right] = \sigma^2_{\widehat{NPV}_{cc,r_{D,j},r_{\bar{D},j}}(u)}, \qquad r_i \le r_j$$

where

$$\sigma^2_{\widehat{NPV}_{cc,r_{D,j},r_{\bar{D},j}}(u)} = \frac{\left(\frac{f_{\bar{D}}\left(F^{-1}(u)\right)}{f(F^{-1}(u))}(1-\rho)\right)^2 \left(NPV(u) + \frac{\rho-u}{u}\right)(1-NPV(u))}{n_D r_{D,j}} + \frac{\left(\frac{f_D\left(F^{-1}(u)\right)}{f(F^{-1}(u))}\rho\right)^2 NPV(u)\left(\frac{1-\rho}{u} - NPV(u)\right)}{n_{\bar{D}} r_{\bar{D},j}}.$$

Proof. It immediate from Theorem 5.1 that $\left(\widehat{PPV}_{cc,r_{D,1},r_{\bar{D},1}}(u), \widehat{PPV}_{cc,r_{D,2},r_{\bar{D},2}}(u), \ldots, \widehat{PPV}_{cc,r_{D,J},r_{\bar{D},J}}(u)\right)$ is approximately multivariate normal with

$$\widehat{PPV}_{cc,r_{D,i},r_{\bar{D},i}}(u) \sim N\left(PPV(u), \sigma^2_{\widehat{PPV}_{cc,r_{D,i},r_{\bar{D},i}}(u)}\right) \qquad i = 1, 2, \ldots, J$$

and

$$Cov\left[\widehat{PPV}_{cc,r_{D,i},r_{\bar{D},i}}(u),\ \widehat{PPV}_{cc,r_{D,j},r_{\bar{D},j}}(u)\right] = Var\left[\widehat{PPV}_{cc,r_{D,j},r_{\bar{D},j}}(u)\right] = \sigma^2_{\widehat{PPV}_{cc,r_{D,j},r_{\bar{D},j}}(u)}, \qquad r_i \le r_j$$

where

$$\sigma^2_{\widehat{PPV}_{cc,r_{D,j},r_{\bar{D},j}}(u)} = \frac{\left(\frac{\rho(1-\rho)}{1-u}\frac{f_{\bar{D}}\left(F^{-1}(u)\right)}{f(F^{-1}(u))}\right)^2 F_D\left(F^{-1}(u)\right)\left(1-F_D\left(F^{-1}(u)\right)\right)}{n_D r_{D,j}} + \frac{\left(\frac{\rho(1-\rho)}{1-u}\frac{f_D\left(F^{-1}(u)\right)}{f(F^{-1}(u))}\right)^2 F_{\bar{D}}\left(F^{-1}(u)\right)\left(1-F_{\bar{D}}\left(F^{-1}(u)\right)\right)}{n_{\bar{D}} r_{\bar{D},j}}.$$

We can write the variance of in terms of $PPV(u)$ by noting that

$$1 - F_D(F^{-1}(u)) = \frac{1-u}{\rho} PPV(u)$$

and

$$1 - F_{\bar{D}}(F^{-1}(u)) = \frac{1-u}{1-\rho}\left(1 - PPV(u)\right),$$

substituting into the above variance formula and simplifying. The proof of part B is nearly identical with the only difference being that we write the variance in terms of $NPV(u)$ by noting that

$$F_D(F^{-1}(u)) = \frac{u}{\rho}\left(1 - NPV(u)\right)$$

and

$$F_{\bar{D}}(F^{-1}(u)) = \frac{u}{1-\rho} NPV(u).$$

□

Corollary 5.4 proves that the sequential empirical estimates of $PPV(u)$ and $NPV(u)$ are asymptotically normal with an independent increments covariance structure. This is an important result as it confirms that existing group sequential methodology can be used to design diagnostic trials using $PPV(u)$ and $NPV(u)$ as the primary outcomes. We are able to derive a normal approximation for the fixed-sample empirical estimates of $PPV(u)$ and $NPV(u)$ as special case of Corollary 5.4.

Corollary 5.5. *Assume A1 - A4 hold and let* $\frac{f_D\left(F^{-1}(u)\right)}{f(F^{-1}(u))}$ *be bounded on* $[a, b]$. *For* $u \in (0, 1)$, *the empirical* *estimates of $PPV(u)$ and $NPV(u)$ are approximately normally distributed with*

$$\widehat{PPV}_{cc,1,1}(u) \sim N\left(PPV(u), \sigma^2_{\widehat{PPV}_{cc,1,1}(u)}\right)$$

and

$$\widehat{NPV}_{cc,1,1}(u) \sim N\left(NPV(u), \sigma^2_{\widehat{NPV}_{cc,1,1}(u)}\right)$$

where $\sigma^2_{\widehat{PPV}_{cc,1,1}(u)}$ and $\sigma^2_{\widehat{NPV}_{cc,1,1}(u)}$ are defined as in Corollary 5.4.

Proof. Immediate from Corollary 5.4. □

5.2 Cohort Sampling

We now consider estimation of the PPV and NPV curve under cohort sampling. Under cohort sampling we must estimate ρ, along with $S_D(x)$ and $F(x)$. The sequential empirical estimate of $PPV(u)$ is defined as

$$\widehat{PPV}_{co,r}(u) = \frac{\hat{S}_{D,r}\left(\hat{F}_r^{-1}(u)\right)\hat{\rho}_r}{1-u}, \tag{50}$$

where $\hat{\rho}_r$, $\hat{S}_{D,r}(x)$ and $\hat{F}_r^{-1}(u)$ are the sequential empirical estimates of ρ, $S_D(x)$ and $F^{-1}(u)$, respectively. We again define the sequential empirical estimate of $NPV(u)$ by substituting the sequential empirical estimate of $PPV(u)$ under cohort sampling into (42),

$$\widehat{NPV}_{co,r}(u) = \frac{u-\rho}{u} + \frac{1-u}{u}\widehat{PPV}_{co,r}(u). \tag{51}$$

Theorem 5.6 establishes the convergence in distribution of $\widehat{PPV}_{co,r}(u)$ to the sum of two independent Kiefer processes. Again, we closely follow the proofs found in Pyke and Shorack (1968).

Theorem 5.6. *Assume A1 - A3 hold,* $\rho \in (0,1)$ *and let* $\frac{f_D\left(F^{-1}(u)\right)}{f(F^{-1}(u))}$ *be bounded on* $[a,b]$*. As* $n \to \infty$

$$\begin{aligned} n^{-1/2}[nr]\left(\widehat{PPV}_{co,r}(u) - PPV(u)\right) \to_D & -\frac{\rho(1-\rho)}{1-u}\frac{f_{\bar{D}}\left(F^{-1}(u)\right)}{f\left(F^{-1}(u)\right)}\frac{1}{\sqrt{\rho}}K_3\left(F_D\left(F^{-1}(u)\right), r\right) \\ & + \frac{\rho(1-\rho)}{1-u}\frac{f_D\left(F^{-1}(u)\right)}{f\left(F^{-1}(u)\right)}\frac{1}{\sqrt{1-\rho}}K_4\left(F_{\bar{D}}\left(F^{-1}(u)\right), r\right) \\ & - \left(\frac{(1-\rho)f_{\bar{D}}\left(F^{-1}(u)\right)}{f\left(F^{-1}(u)\right)}F_D\left(F^{-1}(u)\right) + \frac{\rho f_D\left(F^{-1}(u)\right)}{f\left(F^{-1}(u)\right)}F_{\bar{D}}\left(F^{-1}(u)\right)\right)\frac{\sqrt{\rho(1-\rho)}}{1-u}W(r) \end{aligned}$$

uniformly for $u \in [a,b]$ *and* $r \in [c,1]$ *where* K_3 *and* K_4 *are independent Kiefer Processes and* W *is a Wiener process independent of* K_3 *and* K_4*.*

Proof. First, note that,

$$\begin{aligned} n^{-1/2}[nr]\left(\hat{S}_{D,r}\left(\hat{F}_r^{-1}(u)\right)\hat{\rho}_r - S_D\left(F^{-1}(u)\right)\rho\right) =& n^{-1/2}[nr]\left(F_D\left(F^{-1}(u)\right)\rho - \hat{F}_{D,r}\left(\hat{F}_r^{-1}(u)\right)\hat{\rho}_r\right) \\ =& -F_D\left(F^{-1}(u)\right)n^{-1/2}[nr](\hat{\rho}_r - \rho) \\ & + \hat{\rho}_r n^{-1/2}[nr]\left(F_D\left(F^{-1}(u)\right) - F_D\left(\hat{F}_r^{-1}(u)\right)\right) \\ & - \hat{\rho}_r n^{-1/2}[nr]\left(\hat{F}_{D,r}\left(\hat{F}_r^{-1}(u)\right) - F_D\left(\hat{F}_r^{-1}(u)\right)\right). \end{aligned}$$

The first term converges to a Wiener Process,

$$-F_D\left(F^{-1}(u)\right)n^{-1/2}[nr](\hat{\rho}_r - \rho) \to_D -F_D\left(F^{-1}(u)\right)\sqrt{\rho(1-\rho)}W(r), \tag{52}$$

by Lemma 2.4. It can also be shown that $\hat{\rho}_r \to_{a.s} \rho$ uniformly for $r \in [e,1]$,

$$\begin{aligned} \sup_{e \le r \le 1}|\hat{\rho}_r - \rho| &= \frac{n}{[ne]}\sup_{e \le r \le 1}\frac{[ne]}{n}|\hat{\rho}_r - \rho| \\ &\le \frac{n}{[ne]}\sup_{e \le r \le 1}\frac{[nr]}{n}|\hat{\rho}_r - \rho| \\ &\to_{a.s} 0. \end{aligned}$$

This result can be thought of as a special case of the Glivenko-Cantelli Theorems (1.51 and 1.52 in Csörgő and Szyszkowicz (1998)) for a fixed $x \in (0,1)$, where F is the CDF of a Bernoulli random variable. The second term converges to the sum of two independent Kiefer Proccesses. To see this we rewrite the second term as,

$$
\begin{aligned}
&\hat{\rho}_r n^{-1/2}[nr]\left(F_D\left(F^{-1}(u)\right)-F_D\left(\hat{F}_r^{-1}(u)\right)\right)\\
=&\hat{\rho}_r n^{-1/2}[nr]\frac{F_D\left(F^{-1}(u)\right)-F_D\left(F^{-1}\left(F\left(\hat{F}_r^{-1}(u)\right)\right)\right)}{u-F\left(\hat{F}_r^{-1}(u)\right)}\left(u-F\left(\hat{F}_r^{-1}(u)\right)\right)\\
=&\hat{\rho}_r n^{-1/2}[nr]\frac{F_D\left(F^{-1}\left(F\left(\hat{F}_r^{-1}(u)\right)\right)\right)-F_D\left(F^{-1}(u)\right)}{F\left(\hat{F}_r^{-1}(u)\right)-u}\left(u-\hat{F}_r\left(\hat{F}_r^{-1}(u)\right)\right)\\
&+\hat{\rho}_r n^{-1/2}[nr]\frac{F_D\left(F^{-1}\left(F\left(\hat{F}_r^{-1}(u)\right)\right)\right)-F_D\left(F^{-1}(u)\right)}{F\left(\hat{F}_r^{-1}(u)\right)-u}\left(\hat{F}_r\left(\hat{F}_r^{-1}(u)\right)-F\left(\hat{F}_r^{-1}(u)\right)\right)\\
=&\hat{\rho}_r\frac{F_D\left(F^{-1}\left(F\left(\hat{F}_r^{-1}(u)\right)\right)\right)-F_D\left(F^{-1}(u)\right)}{F\left(\hat{F}_r^{-1}(u)\right)-u}n^{-1/2}[nr]\left(u-\hat{F}_r\left(\hat{F}_r^{-1}(u)\right)\right)\\
&+\hat{\rho}_r\frac{F_D\left(F^{-1}\left(F\left(\hat{F}_r^{-1}(u)\right)\right)\right)-F_D\left(F^{-1}(u)\right)}{F\left(\hat{F}_r^{-1}(u)\right)-u}n^{-1/2}[nr]\left(\hat{\rho}_r\hat{F}_{D,r_D}\left(\hat{F}_r^{-1}(u)\right)-\rho F_D\left(\hat{F}_r^{-1}(u)\right)\right)\\
&+\hat{\rho}_r\frac{F_D\left(F^{-1}\left(F\left(\hat{F}_r^{-1}(u)\right)\right)\right)-F_D\left(F^{-1}(u)\right)}{F\left(\hat{F}_r^{-1}(u)\right)-u}n^{-1/2}[nr]\left((1-\hat{\rho}_r)\hat{F}_{\bar{D},r_{\bar{D}}}\left(\hat{F}_r^{-1}(u)\right)-(1-\rho)F_{\bar{D}}\left(\hat{F}_r^{-1}(u)\right)\right)\\
=&\hat{\rho}_r\frac{F_D\left(F^{-1}\left(F\left(\hat{F}_r^{-1}(u)\right)\right)\right)-F_D\left(F^{-1}(u)\right)}{F\left(\hat{F}_r^{-1}(u)\right)-u}n^{-1/2}[nr]\left(u-\hat{F}_r\left(\hat{F}_r^{-1}(u)\right)\right)\\
&+\hat{\rho}_r\frac{F_D\left(F^{-1}\left(F\left(\hat{F}_r^{-1}(u)\right)\right)\right)-F_D\left(F^{-1}(u)\right)}{F\left(\hat{F}_r^{-1}(u)\right)-u}\hat{\rho}_r n^{-1/2}[nr]\left(\hat{F}_{D,r_D}\left(\hat{F}_r^{-1}(u)\right)-F_D\left(\hat{F}_r^{-1}(u)\right)\right)\\
&+\hat{\rho}_r\frac{F_D\left(F^{-1}\left(F\left(\hat{F}_r^{-1}(u)\right)\right)\right)-F_D\left(F^{-1}(u)\right)}{F\left(\hat{F}_r^{-1}(u)\right)-u}(1-\hat{\rho}_r)n^{-1/2}[nr]\left(\hat{F}_{\bar{D},r_{\bar{D}}}\left(\hat{F}_r^{-1}(u)\right)-F_{\bar{D}}\left(\hat{F}_r^{-1}(u)\right)\right)\\
&+\hat{\rho}_r\frac{F_D\left(F^{-1}\left(F\left(\hat{F}_r^{-1}(u)\right)\right)\right)-F_D\left(F^{-1}(u)\right)}{F\left(\hat{F}_r^{-1}(u)\right)-u}\left(F_D\left(\hat{F}_r^{-1}(u)\right)-F_{\bar{D}}\left(\hat{F}_r^{-1}(u)\right)\right)n^{-1/2}[nr](\hat{\rho}_r-\rho)
\end{aligned}
$$

We must show that $\frac{F_D\left(F^{-1}\left(F\left(\hat{F}_r^{-1}(u)\right)\right)\right)-F_D\left(F^{-1}(u)\right)}{F\left(\hat{F}_r^{-1}(u)\right)-u}$ converges uniformly to $\frac{f_D\left(F^{-1}(u)\right)}{f\left(F^{-1}(u)\right)}$ for $r\in[e,1]$ and $u\in[a,b]$. A simple application of the Glivenko-Cantelli Theorems (1.51 and 1.52 in Csörgő and Szyszkowicz (1998)) allows us to conclude that $F\left(\hat{F}_r^{-1}(u)\right)$ converges to u uniformly,

$$
\begin{aligned}
\sup_{e\le r\le 1}\sup_{a\le u\le b}\left|F\left(\hat{F}_r^{-1}(u)\right)-u\right| &= \frac{n}{[ne]}\sup_{e\le r\le 1}\sup_{a\le u\le b}\frac{[ne]}{n}\left|F\left(\hat{F}_r^{-1}(u)\right)-u\right|\\
&\le \frac{n}{[ne]}\sup_{e\le r\le 1}\sup_{a\le u\le b}\frac{[nr]}{n}\left|F\left(\hat{F}_r^{-1}(u)\right)-u\right|\\
&\to_{a.s}0. \qquad (53)
\end{aligned}
$$

We note that (53) also implies that $F_D\left(\hat{F}_r^{-1}(u)\right)$ and $F_{\bar{D}}\left(\hat{F}_r^{-1}(u)\right)$ converge uniformly to $F_D\left(F^{-1}(u)\right)$ and $F_{\bar{D}}\left(F^{-1}(u)\right)$, respectively, which can be seen by noting that the difference between $F_D\left(\hat{F}_r^{-1}(u)\right)$ and $F_D\left(F^{-1}(u)\right)$ will always have the same sign as the difference between $F_{\bar{D}}\left(\hat{F}_r^{-1}(u)\right)$ and $F_{\bar{D}}\left(F^{-1}(u)\right)$.

By the mean value theorem, there exists $F\left(\tilde{F}_r^{-1}(u)\right)$ between u and $F\left(\hat{F}_r^{-1}(u)\right)$, such that,

$$\frac{F_D\left(F^{-1}\left(F\left(\hat{F}_r^{-1}(u)\right)\right)\right)-F_D\left(F^{-1}(u)\right)}{F\left(\hat{F}_r^{-1}(u)\right)-u}=\frac{f_D\left(F^{-1}\left(F\left(\tilde{F}_r^{-1}(u)\right)\right)\right)}{f\left(F^{-1}\left(F\left(\tilde{F}_r^{-1}(u)\right)\right)\right)}.$$

Since $F\left(\tilde{F}_r^{-1}(u)\right)\rightarrow_{a.s.}u$ uniformly and by the uniform continuity of $\frac{f_D\left(F^{-1}(u)\right)}{f\left(F^{-1}(u)\right)}$,

$$\sup_{e<r\leq 1}\sup_{a\leq u\leq b}\left|\frac{f_D\left(F^{-1}\left(F\left(\tilde{F}_r^{-1}(u)\right)\right)\right)}{f\left(F^{-1}\left(F\left(\tilde{F}_r^{-1}(u)\right)\right)\right)}-\frac{f_D\left(F^{-1}(u)\right)}{f\left(F^{-1}(u)\right)}\right|\rightarrow_{a.s.}0,$$

which implies,

$$\frac{F_D\left(F^{-1}\left(F\left(\hat{F}_r^{-1}(u)\right)\right)\right)-F_D\left(F^{-1}(u)\right)}{F\left(\hat{F}_r^{-1}(u)\right)-u}\rightarrow_{a.s}\frac{f_D\left(F^{-1}(u)\right)}{f\left(F^{-1}(u)\right)},\tag{54}$$

uniformly for $u\in[a,b]$ and $r\in[e,1]$. For all $r\in[e,1]$,

$$\sup_{a\leq u\leq b}n^{-1/2}[nr]\left|u-\hat{F}_r\left(\hat{F}_r^{-1}(u)\right)\right|\leq_{a.s.}\frac{1}{n^{1/2}}.$$

Therefore, as $n\rightarrow\infty$,

$$\sup_{e\leq r\leq 1}\sup_{a\leq u\leq b}n^{-1/2}[nr]\left|u-\hat{F}_r\left(\hat{F}_r^{-1}(u)\right)\right|\rightarrow_{a.s.}0.$$

From this result, (54) and the uniform convergence of $\hat{\rho}_r$ to ρ we can conclude that,

$$\hat{\rho}_r\frac{F_D\left(F^{-1}\left(F\left(\hat{F}_r^{-1}(u)\right)\right)\right)-F_D\left(F^{-1}(u)\right)}{F\left(\hat{F}_r^{-1}(u)\right)-u}n^{-1/2}[nr]\left(u-\hat{F}_r\left(\hat{F}_r^{-1}(u)\right)\right)\rightarrow_{a.s.}0,$$

uniformly for $u\in[a,b]$ and $r\in[e,1]$. From (54), the uniform convergence of $\hat{\rho}_r$ to ρ, Lemma 2.4 and the uniform continuity of the Kiefer process we can conclude,

$$\hat{\rho}_r \frac{F_D\left(F^{-1}\left(F\left(\hat{F}_r^{-1}(u)\right)\right)\right) - F_D\left(F^{-1}(u)\right)}{F\left(\hat{F}_r^{-1}(u)\right) - u} \hat{\rho}_r n^{-1/2}[nr]\left(\hat{F}_{D,r_D}\left(\hat{F}_r^{-1}(u)\right) - F_D\left(\hat{F}_r^{-1}(u)\right)\right)$$
$$\to_D \frac{\rho^2 f_D\left(F^{-1}(u)\right)}{f\left(F^{-1}(u)\right)} \frac{1}{\sqrt{\rho}} K_3\left(F_D\left(F^{-1}(u)\right), r\right), \qquad (55)$$

$$\hat{\rho}_r \frac{F_D\left(F^{-1}\left(F\left(\hat{F}_r^{-1}(u)\right)\right)\right) - F_D\left(F^{-1}(u)\right)}{F\left(\hat{F}_r^{-1}(u)\right) - u} (1-\hat{\rho}_r) n^{-1/2}[nr]\left(\hat{F}_{\bar{D},r_{\bar{D}}}\left(\hat{F}_r^{-1}(u)\right) - F_{\bar{D}}\left(\hat{F}_r^{-1}(u)\right)\right)$$
$$\to_D \frac{\rho(1-\rho) f_D\left(F^{-1}(u)\right)}{f\left(F^{-1}(u)\right)} (1-\rho) \frac{1}{\sqrt{1-\rho}} K_3\left(F_{\bar{D}}\left(F^{-1}(u)\right), r\right), \qquad (56)$$

and

$$\hat{\rho}_r \frac{F_D\left(F^{-1}\left(F\left(\hat{F}_r^{-1}(u)\right)\right)\right) - F_D\left(F^{-1}(u)\right)}{F\left(\hat{F}_r^{-1}(u)\right) - u} \left(F_D\left(\hat{F}_r^{-1}(u)\right) - F_{\bar{D}}\left(\hat{F}_r^{-1}(u)\right)\right) n^{-1/2}[nr](\hat{\rho}_r - \rho)$$
$$\to_D \frac{\rho f_D\left(F^{-1}(u)\right)}{f\left(F^{-1}(u)\right)} \left(F_D\left(F^{-1}(u)\right) - F_{\bar{D}}\left(F^{-1}(u)\right)\right) \sqrt{\rho(1-\rho)} W(r), \qquad (57)$$

where K_3 and K_4 are Kiefer processes and W is the same Wiener Process from (52) and is independent of K_3 and K_4. The third term converges in distribution to a Kiefer process,

$$-\hat{\rho}_r n^{-1/2}[nr]\left(\hat{F}_{D,r}\left(\hat{F}_r^{-1}(u)\right) - F_D\left(\hat{F}_r^{-1}(u)\right)\right) \to_D -\rho \frac{1}{\sqrt{\rho}} K_3\left(F_D\left(F^{-1}(u)\right), r\right), \qquad (58)$$

by Lemma 2.4, the uniform continuity of the Kiefer process and the uniform convergence of $\hat{\rho}_R$ to ρ. Summing (52), (55), (56), (57),(58) and some algebra gives the desired result. □

Theorem 5.6 establishes distribution theory for the sequential empirical PPV curve indexed by the percentile value. From this result we can easily develop distribution theory for the fixed-sample empirical PPV curve, the sequential empirical NPV curve and the fixed-sample empirical NPV curve. Corollary 5.7 considers the fixed-sample empirical PPV curve as a special case, while Corollary 5.8 establishes distribution theory for the sequential and fixed-sample empirical NPV curve indexed by the percentile value.

Corollary 5.7. *Assume A1 - A3 hold, $\rho \in (0,1)$ and let $\frac{f_D(F^{-1}(u))}{f(F^{-1}(u))}$ be bounded on $[a,b]$. As $n \to \infty$*

$$\begin{aligned} n^{1/2}\left(\widehat{PPV}_{co,1}(u) - PPV(u)\right) \to_D & -\frac{\rho(1-\rho)}{1-u}\frac{f_{\bar D}\left(F^{-1}(u)\right)}{f\left(F^{-1}(u)\right)}\frac{1}{\sqrt{\rho}}B_3\left(F_D\left(F^{-1}(u)\right)\right) \\ & + \frac{\rho(1-\rho)}{1-u}\frac{f_D\left(F^{-1}(u)\right)}{f\left(F^{-1}(u)\right)}\frac{1}{\sqrt{1-\rho}}B_4\left(F_{\bar D}\left(F^{-1}(u)\right)\right) \\ & - \left(\frac{(1-\rho)f_{\bar D}\left(F^{-1}(u)\right)}{f\left(F^{-1}(u)\right)}F_D\left(F^{-1}(u)\right) + \frac{\rho f_D\left(F^{-1}(u)\right)}{f\left(F^{-1}(u)\right)}F_{\bar D}\left(F^{-1}(u)\right)\right)\frac{\sqrt{\rho(1-\rho)}}{1-u}Z \end{aligned}$$

uniformly for $u \in [a,b]$ where B_3 and B_3 are independent Brownian Bridges and Z is a standard normal random variable independent of B_3 and B_4.

Proof. Immediate from Theorem 5.6 and by noting that $K(t,1) =_D B(t)$. □

Corollary 5.8. *Assume A1 - A3 hold, $\rho \in (0,1)$ and let $\frac{f_D(F^{-1}(u))}{f(F^{-1}(u))}$ be bounded on $[a,b]$. As $n \to \infty$*

$$\begin{aligned} n^{-1/2}[nr]\left(\widehat{NPV}_{co,r}(u) - NPV(u)\right) \to_D & -\frac{\rho(1-\rho)}{u}\frac{f_{\bar D}\left(F^{-1}(u)\right)}{f\left(F^{-1}(u)\right)}\frac{1}{\sqrt{\rho}}K_3\left(F_D\left(F^{-1}(u)\right), r\right) \\ & + \frac{\rho(1-\rho)}{u}\frac{f_D\left(F^{-1}(u)\right)}{f\left(F^{-1}(u)\right)}\frac{1}{\sqrt{1-\rho}}K_4\left(F_{\bar D}\left(F^{-1}(u)\right), r\right) \\ & - \left(\frac{(1-\rho)f_{\bar D}\left(F^{-1}(u)\right)}{f\left(F^{-1}(u)\right)}F_D\left(F^{-1}(u)\right) + \frac{\rho f_D\left(F^{-1}(u)\right)}{f\left(F^{-1}(u)\right)}F_{\bar D}\left(F^{-1}(u)\right)\right)\frac{\sqrt{\rho(1-\rho)}}{u}W(r) \end{aligned}$$

uniformly for $u \in [a,b]$, $r \in [e,1]$ where K_3 and K_4 are independent Kiefer Processes and W is a Wiener process independent of K_3 and K_4.

$$\begin{aligned} n^{1/2}\left(\widehat{NPV}_{co,1}(u) - PPV(u)\right) \to_D & -\frac{\rho(1-\rho)}{u}\frac{f_{\bar D}\left(F^{-1}(u)\right)}{f\left(F^{-1}(u)\right)}\frac{1}{\sqrt{\rho}}B_1\left(F_D\left(F^{-1}(u)\right)\right) \\ & + \frac{\rho(1-\rho)}{u}\frac{f_D\left(F^{-1}(u)\right)}{f\left(F^{-1}(u)\right)}\frac{1}{\sqrt{1-\rho}}B_2\left(F_{\bar D}\left(F^{-1}(u)\right)\right) \\ & - \left(\frac{(1-\rho)f_{\bar D}\left(F^{-1}(u)\right)}{f\left(F^{-1}(u)\right)}F_D\left(F^{-1}(u)\right) + \frac{\rho f_D\left(F^{-1}(u)\right)}{f\left(F^{-1}(u)\right)}F_{\bar D}\left(F^{-1}(u)\right)\right)\frac{\sqrt{\rho(1-\rho)}}{u}Z \end{aligned}$$

uniformly for $u \in [a,b]$ where B_3 and B_3 are independent Brownian Bridges and Z is a standard normal random variable independent of B_3 and B_4.

Proof. Immediate from Theorem 5.6, Corollary 5.7 and (42). □

Theorem 5.6, Corollary 5.7 and Corollary 5.8 establish the convergence of the fixed-sample and sequential empirical PPV and NPV curve indexed by the percentile value under cohort sampling. These results allow us to develop distribution theory for summaries of the PPV and NPV curves. Corollary 5.9 establishes that the sequential empirical estimates of $PPV(u)$ and $NPV(u)$, a point on the PPV and NPV curve, respectively, are asymptotically normal with an independent increments covariance structure.

Corollary 5.9. *Assume A1 - A3 hold, $\rho \in (0,1)$ and let $\frac{f_D\left(F^{-1}(u)\right)}{f(F^{-1}(u))}$ be bounded on $[a,b]$. For $u \in (0,1)$ and J stopping times,*

A. $\left(\widehat{PPV}_{co,r_1}(u), \widehat{PPV}_{co,r_2}(u), \ldots, \widehat{PPV}_{co,r_J}(u)\right)$, *is approximately multivariate normal with,*

$$\widehat{PPV}_{co,r_i}(u) \sim N\left(PPV(u), \sigma^2_{\widehat{PPV}_{co,r_i}(u)}\right) \qquad i = 1,2,\ldots,J$$

and

$$Cov\left[\widehat{PPV}_{co,r_i}(u), \widehat{PPV}_{co,r_j}(u)\right] = Var\left[\widehat{PPV}_{co,r_j}(u)\right] = \sigma^2_{\widehat{PPV}_{co,r_j}(u)}, \qquad r_i \leq r_j$$

where

$$\begin{aligned}\sigma^2_{\widehat{PPV}_{co,r_j}(u)} =& \frac{\left(\frac{f_{\bar{D}}\left(F^{-1}(u)\right)}{f\left(F^{-1}(u)\right)}(1-\rho)\right)^2 PPV(u)\left(\frac{\rho}{1-u} - PPV(u)\right)}{\rho n r_j} \\ &+ \frac{\left(\frac{f_D\left(F^{-1}(u)\right)}{f\left(F^{-1}(u)\right)}\rho\right)^2 (1-PPV(u))\left(\frac{u-\rho}{1-u} + PPV(u)\right)}{(1-\rho)\, n r_j} \\ &+ \frac{\left(PPV(u)\left(\frac{f_D\left(F^{-1}(u)\right)}{(1-\rho) f\left(F^{-1}(u)\right)} - \frac{1}{\rho}\right) + \frac{1}{1-u} - \frac{\rho f_D\left(F^{-1}(u)\right)}{(1-\rho) f\left(F^{-1}(u)\right)}\right)^2 \rho(1-\rho)}{nr}.\end{aligned}$$

B. $\left(\widehat{NPV}_{co,r_1}(u), \widehat{NPV}_{co,r_2}(u), \ldots, \widehat{NPV}_{co,r_J}(u)\right)$, *is approximately multivariate normal with,*

$$\widehat{NPV}_{co,r_i}(u) \sim N\left(NPV(u), \sigma^2_{\widehat{NPV}_{co,r_i}(u)}\right) \qquad i = 1,2,\ldots,J$$

and

$$Cov\left[\widehat{NPV}_{co,r_i}(u), \widehat{NPV}_{co,r_j}(u)\right] = Var\left[\widehat{NPV}_{co,r_j}(u)\right] = \sigma^2_{\widehat{NPV}_{co,r_j}(u)}, \qquad r_i \leq r_j$$

where

$$\sigma^2_{\widehat{NPV}_{co,r_j}(u)} = \frac{\left(\frac{f_{\bar{D}}\left(F^{-1}(u)\right)}{f\left(F^{-1}(u)\right)}(1-\rho)\right)^2 \left(NPV(u)+\frac{\rho-u}{u}\right)(1-NPV(u))}{\rho n r_j} + \frac{\left(\frac{f_D\left(F^{-1}(u)\right)}{f\left(F^{-1}(u)\right)}\rho\right)^2 NPV(u)\left(\frac{1-\rho}{u}-NPV(u)\right)}{(1-\rho)\, n r_j} + \frac{\left(NPV(u)\left(\frac{f_D\left(F^{-1}(u)\right)}{(1-\rho) f\left(F^{-1}(u)\right)}-\frac{1}{\rho}\right)+\frac{1}{\rho}-\frac{f_D\left(F^{-1}(u)\right)}{f\left(F^{-1}(u)\right)}\right)^2 \rho(1-\rho)}{nr}.$$

Proof. It immediate from Theorem 5.6 that $\left(\widehat{PPV}_{co,r_1}(u), \widehat{PPV}_{co,r_2}(u), \ldots, \widehat{PPV}_{co,r_J}(u)\right)$ is approximately multivariate normal with

$$\widehat{PPV}_{co,r_i}(u) \sim N\left(PPV(u), \sigma^2_{\widehat{PPV}_{co,r_i}(u)}\right) \qquad i = 1, 2, \ldots, J$$

and

$$Cov\left[\widehat{PPV}_{co,r_i}(u), \widehat{PPV}_{co,r_j}(u)\right] = Var\left[\widehat{PPV}_{co,r_j}(u)\right] = \sigma^2_{\widehat{PPV}_{co,r_j}(u)}, \qquad r_i \le r_j$$

where

$$\sigma^2_{\widehat{PPV}_{co,r_j}(u)} = \frac{\left(\frac{\rho(1-\rho)}{1-u}\frac{f_{\bar{D}}\left(F^{-1}(u)\right)}{f\left(F^{-1}(u)\right)}\right)^2 F_D\left(F^{-1}(u)\right)\left(1-F_D\left(F^{-1}(u)\right)\right)}{\rho n r_j} + \frac{\left(\frac{\rho(1-\rho)}{1-u}\frac{f_D\left(F^{-1}(u)\right)}{f\left(F^{-1}(u)\right)}\right)^2 F_{\bar{D}}\left(F^{-1}(u)\right)\left(1-F_{\bar{D}}\left(F^{-1}(u)\right)\right)}{(1-\rho)\, n r_j} + \frac{\left(\frac{(1-\rho) f_{\bar{D}}\left(F^{-1}(u)\right)}{(1-u) f\left(F^{-1}(u)\right)} F_D\left(F^{-1}(u)\right) + \frac{\rho f_D\left(F^{-1}(u)\right)}{(1-u) f\left(F^{-1}(u)\right)} F_{\bar{D}}\left(F^{-1}(u)\right)\right)^2 \rho(1-\rho)}{nr}.$$

We can write the variance in terms of $PPV(u)$ by noting that

$$1 - F_D(F^{-1}(u)) = \frac{1-u}{\rho} PPV(u)$$

and

$$1 - F_{\bar{D}}(F^{-1}(u)) = \frac{1-u}{1-\rho}(1 - PPV(u)),$$

substituting into the above variance formula and simplifying. The proof of part B is nearly identical with the only difference being that we write the variance in terms of $NPV(u)$ by noting that

$$F_D(F^{-1}(u)) = \frac{u}{\rho}(1 - NPV(u))$$

and

$$F_{\bar{D}}(F^{-1}(u)) = \frac{u}{1-\rho} NPV(u).$$

$\square$

Finally, Corollary 5.10 establishes a normal approximation for the fixed-sample empirical estimates of $PPV(u)$ and $NPV(u)$ under cohort sampling as a special case of Corollary 5.9.

Corollary 5.10. *Assume A1 - A3 hold, $\rho \in (0,1)$ and let $\frac{f_D(F^{-1}(u))}{f(F^{-1}(u))}$ be bounded on $[a,b]$. For $u \in (0,1)$, the empirical estimates of $PPV(u)$ and $NPV(u)$ are approximately normally distributed with*

$$\widehat{PPV}_{co,1}(u) \sim N\left(PPV(u), \sigma^2_{\widehat{PPV}_{co,1}(u)}\right)$$

and

$$\widehat{NPV}_{co,1}(u) \sim N\left(NPV(u), \sigma^2_{\widehat{NPV}_{co,1}(u)}\right)$$

where $\sigma^2_{\widehat{PPV}_{co,1}(u)}$ and $\sigma^2_{\widehat{NPV}_{co,1}(u)}$ are defined as in Corollary 5.4.

Proof. Immediate from Corollary 5.9. $\square$

6 Discussion

We considered the asymptotic properties of the sequential empirical ROC, PPV and NPV curves. We first extended the work of Hsieh and Turnbull (1996) to the sequential empirical ROC curve. We showed that the sequential empirical ROC curve converges to the sum of independent Kiefer processes and that the sequential empirical estimate of a point on the ROC curve is asymptotically normal with an independent increments covariance structure. Next, distribution theory was developed for the sequential empirical PPV and NPV curves indexed by the true positive fraction, false positive fraction and the percentile value in the entire population. In all cases, the sequential empirical PPV and NPV curves converge to the sum of independent Kiefer processes and the sequential empirical estimate of a point on the PPV and NPV curve is asymptotically normal with an independent increments covariance structure. Finally, distribution theory for the fixed-sample empirical PPV and NPV curves were developed as a special case.

The results in this chapter provide the theoretical basis for applying standard group sequential methods to diagnostic biomarker studies. The independent increments assumption is common in the group sequential testing literature. Verifying that the independent increments assumption holds for the sequential empirical estimate of a point on the ROC, PPV and NPV curves allows us to use standard group sequential methods with a point a point on the ROC, PPV or NPV curve as our summary of interest. Furthermore, the results in this chapter apply to the entire process which will allow us to easily develop distribution theory for other summaries of the ROC, PPV and NPV curves.

We showed that the sequential empirical estimate of a point on the ROC, PPV or NPV curve has an independent increments covariance structure. This is only one of many summaries of the ROC, PPV or NPV curve. Future work is needed to show that this assumption holds for other summary measures and to identify summary measures for which the independent increments assumption does not hold. For example, the area under the ROC curve (AUC) is a common summary measure of the ROC curve and it would be beneficial to show that the independent increments assumption holds for the sequential empirical estimate of the AUC. Also, the results in this chapter only deal with the estimation of the ROC, PPV or NPV curve for a single marker. In many cases we estimate the ROC, PPV or NPV curve for multiple markers and compare the performance of these markers by comparing summaries of the ROC, PPV or NPV curve. Future work is needed to generalize the results in this chapter to the cases with multiple markers and arbitrary correlation between markers.

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