**SUPPLEMENTAL INFORMATION**

Let denote sensitivity as x (0<x<1), specificity as y (0<y<1), prevalence as p (0<p<1), positive predictive value (PPV) as f, and negative predictive value (NPV) as g, we have:

* $f=f\left(x, y, p\right)= \frac{xp}{xp+(1-y)(1-p)}$ (1)
* $g=g\left(x, y, p\right)= \frac{y(1-p)}{y\left(1-p\right)+p(1-x)}$ (2)

**1) Relationship between PPV and prevalence:**

To investigate the relationship between PPV (f) and prevalence (p), we consider the following:

* $\frac{∂f}{∂p}=\frac{-x(y-1)}{\left(px-y-p+py+1\right)^{2}}$ (3)
* $\frac{∂^{2}f}{∂p^{2}}=\frac{2x(y-1)(x+y-1)}{\left(px-y-p+py+1\right)^{3}}$ (4)

Given x, y, and p are between 0 and 1, (y-1) must be ≤0 and thus, -x(y-1) is ≥0. Furthermore, (px-y-p+py+1)2 is always non-negative and thus, $\frac{∂f}{∂p}$ is ≥0.

We examine the denominator of equation (4). We have:

* $px-y-p+py+1=p\left(x+y-1\right)-(y-1)$

This suggests that $\frac{∂^{2}f}{∂p^{2}}$ depends on (x+y-1). If x+y-1≥0 and y-1≤0 (based on the boundary of y), then p(x+y-1)-(y-1)≥0. Hence, $\frac{∂^{2}f}{∂p^{2}}$≤0 and thus, f is a concave function with respect to p (when x+y-1≥0).

On the other hand, if x+y-1<0 and p is between 0 and 1, we have:

* $x+y-1\geq \frac{x+y-1}{p}=\frac{x}{p}+\frac{y-1}{p}\geq \frac{y-1}{p}$
* $p\left(x+y-1\right)\geq y-1$
* $p\left(x+y-1\right)-(y-1)\geq 0$

Hence, when x+y-1<0, $\frac{∂^{2}f}{∂p^{2}}$≥0 and thus, PPV (f) is a convex function with respect to prevalence (p, Supplemental Figure 1).

**2) Relationship between PPV and sensitivity:**

To investigate the relationship between PPV (f) and sensitivity (x), we consider the following:

* $\frac{∂f}{∂x}=\frac{p(p-1)(y-1)}{\left(px-y-p+py+1\right)^{2}}$ (5)
* $\frac{∂^{2}f}{∂x^{2}}=\frac{-2p^{2}(p-1)(y-1)}{\left(px-y-p+py+1\right)^{3}}$ (6)

Given x, y, and p are non-negative, (p-1) and (y-1) must be ≤0. Furthermore, (px-y-p+py+1)2 is always non-negative and thus, $\frac{∂f}{∂x}$≥0.

As suggested in section 1 above (equation 4), px-y-p+py+1≥0. Hence, $\frac{∂^{2}f}{∂x^{2}}\leq $0 and thus, PPV (f) is a concave function with respect to sensitivity (x, Supplemental Figure 2)

**3) Relationship between PPV and specificity:**

To investigate the relationship between PPV (f) and specificity (y), we consider the following:

* $\frac{∂f}{∂y}=\frac{-px(p-1)}{\left(\left(p-1\right)\left(y-1\right)+px\right)^{2}}$ (7)
* $\frac{∂^{2}f}{∂y^{2}}=\frac{2px\left(p-1\right)^{2}}{\left(\left(p-1\right)\left(y-1\right)+px\right)^{3}}$ (8)

Given x, y, and p are non-negative, (p-1) must be ≤0 and thus, -px(p-1) must be ≥0. Furthermore, ((p-1)(y-1)+px)2 is always non-negative and thus, $\frac{∂f}{∂y}$≥0.

Similarly, 2px(p-1)2 is always non-negative. Moreover, (p-1)(y-1) is ≥0 and therefore, (p-1)(y-1)+px is always non-negative and thus, $\frac{∂^{2}f}{∂y^{2}}$ ≥0. Hence, PPV (f) is a convex function with respect to sensitivity (y, Supplemental Figure 3).

**4) Relationship between NPV and prevalence:**

To investigate the relationship between NPV (g) and prevalence (p), we consider the following:

* $\frac{∂g}{∂p}=\frac{y(x-1)}{\left(p+y-px-py\right)^{2}}$ (9)
* $\frac{∂^{2}g}{∂p^{2}}=\frac{2y(x-1)(x+y-1)}{\left(p+y-px-py\right)^{3}}$ (10)

Given x, y, and p are non-negative, (x-1) must be ≤0 and thus, y(x-1) is always ≤0. Furthermore, (p+y-px-py)2 is always ≥0 and thus, $\frac{∂g}{∂p}$≤0.

We examine equation (10) by evaluating its denominator:

* $p+y-px-py=p\left(1-x\right)-y(p-1)$

Given the boundary conditions of x, y, and p between 0 and 1, (1-x) is ≥0 and (p-1) is ≤0. Hence, p(1-x)-y(p-1) (or p+y-px-py) is always ≥0. Therefore, the value of $\frac{∂^{2}g}{∂p^{2}}$ depends on x+y-1. If x+y-1≥0, then $\frac{∂^{2}g}{∂p^{2}}$≤0 (and thus, NPV (g) is a concave function with respect to prevalence [p]), and vice versa, if x+y-1<0, then $\frac{∂^{2}g}{∂p^{2}}$>0 (and thus, NPV (g) is a convex function with respect to prevalence [p], Supplemental Figure 1).

**5) Relationship between NPV and sensitivity:**

To investigate the relationship between NPV (g) and sensitivity (x), we consider the following:

* $\frac{∂g}{∂x}=\frac{py(1-p)}{\left(p\left((1-x)\right)+y(1-p)\right)^{2}}$ (11)
* $\frac{∂^{2}g}{∂x^{2}}=\frac{2p^{2}y(1-p)}{\left(p\left(1-x\right)+y(1-p)\right)^{3}}$ (12)

Given x, y, and p are non-negative values, (1-p) must be ≥0 and thus, py(1-p) must be ≥0. Furthermore, (p(1-x)+y(1-p))2 is always non-negative and thus, $\frac{∂g}{∂x}$ is ≥0.

Similarly, 2p2y(1-p) is always ≥0. Moreover, (1-x) and (1-p) are ≥0 and thus, p(1-x)+y(1-p) is non-negative. Hence, p(x-1)+y(p-1) is always non-negative and thus, $\frac{∂^{2}g}{∂x^{2}}$ ≥0. Hence, NPV (g) is a convex function with respect to sensitivity (x, Supplemental Figure 2).

**6) Relationship between NPV and specificity:**

To investigate the relationship between NPV (g) and specificity (y), we consider the following:

* $\frac{∂g}{∂y}=\frac{p(p-1)(x-1)}{\left(p+y-px-py\right)^{2}}$ (13)
* $\frac{∂^{2}g}{∂y^{2}}=\frac{2p\left(p-1\right)^{2}(x-1)}{\left(p+y-px-py\right)^{3}}$ (14)

Given x, y, and p are non-negative values, (x-1) and (p-1) must be ≤0 and thus, p(p-1)(x-1) is ≥0. Furthermore, (p+y-px-py)2 is always non-negative and thus, $\frac{∂g}{∂y}$≥0.

As shown in section (4) above (equation 10), p+y-px-py is always ≥0. Furthermore, x-1 must be ≤0 and hence, 2p(p-1)2(x-1)≤0. Thus, $\frac{∂^{2}g}{∂y^{2}}$≤0 and NPV (g) is a concave function with respect to specificity (y, Supplemental Figure 3).

**Supplemental Figure S1**: PPV and NPV as a function of prevalence (while keeping sensitivity and specificity constant). PPV (solid red line) and NPV (blue line with stars) were constructed using a sensitivity of 95% and a specificity of 90%. Similarly, a second PPV (green line with circles) and NPV (black line with triangles) were constructed using a sensitivity of 75% and a specificity of 70%. As seen, the prevalence drives significant rate of increase in PPV at the low end (of prevalence) and significant rate of decrease in NPV at the high end (of prevalence).



**Supplemental Figure S2**: PPV and NPV as a function of sensitivity (while keeping the prevalence and specificity constant). PPV (solid red line) and NPV (blue line with stars) were constructed using a prevalence of 10% and a specificity of 90%. Similarly, a second PPV (green line with circles) and NPV (black line with triangles) were constructed using a prevalence of 40% and a specificity of 90%. As seen, at a prevalence of 10%, the effect of sensitivity on PPV diminishes as the sensitivity increased beyond ~60% (solid red line) while the NPV increased at a higher rate (blue line with stars). These effects are more dramatically observed with a higher prevalence of 40% (black line with triangles).



**Supplemental Figure S3**: PPV and NPV as a function of specificity (while keeping the prevalence and sensitivity constant). PPV (solid red line) and NPV (blue line with stars) were constructed using a prevalence of 10% and a sensitivity of 95%. Similarly, a second PPV (green line with circles) and NPV (black line with triangles) were constructed using a prevalence of 40% and a sensitivity of 95%. As seen, at a prevalence of 10%, the effect of sensitivity on PPV increased dramatically after the specificity >~80% (solid red line). However, the specificity virtually has no impact on the NPV when the specificity >~20% (blue line with stars). These effects are also seen when the prevalence is higher (at 40%) but less dramatic.

