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# Reconstructed human Epidermis Test Methods for Skin Corrosion Endpoint: How Can Changes in Prediction Models Improve Final Predictions?

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## Introduction

- In the context of **OECD TG 431**, *in vitro* test methods based on Reconstructed human Epidermis (RHE) derived from human epidermal keratinocytes are used to assess the **skin corrosion potential of chemicals**. Four test methods are covered by OECD TG 431 i.e., **EpiSkin™**, **EpiDerm™**, **SkinEthic™ RHE** and **epiCS® Skin Corrosion Tests**.
- OECD TG 431 allows for partial sub-categorization of chemicals to **UN GHS Category 1A, combined Category 1B/1C or Non-Corrosive**, on the basis of **tissue viabilities** obtained after **3 min** and **60 min exposures** and additionally 240 min for EpiSkin™.
- The over-prediction rate obtained for Category 1B/1C with EpiDerm™, SkinEthic™ and epiCS® using the currently accepted Prediction Model is close to 50%.
- The current study explored possible **variations of the Prediction Model** in order to improve the overall accuracy of EpiDerm™, SkinEthic™ and epiCS®.

## Two new Prediction Models (PM) developed on the basis the tissue viabilities obtained after 3 min (v3) and 60 min (v60) exposure.

**Current Prediction Model** as included in TG 431

v3<50%	→	Category 1A
v3≥50% AND v60<15%	→	Category 1B/1C
v3≥50% AND v60 ≥15%	→	Non-Corrosive

**Prediction Model, Variation 1 (PMvar1):** PMvar1 is based on a 2-step approach

<b>Step1:</b> Corr. vs. Non-Corr.	{v3<50} OR {v3≥50 AND v60<15} → <b>Corr.</b>	v3≥50 AND v60≥15 → <b>Non-Corr.</b>
<b>Step2:</b> Cat. 1A vs. Cat. 1B/1C	v3<x → <b>Cat. 1A</b>	v3≥x → <b>Cat. 1B/1C</b>

**Prediction Model, Variation 2 (PMvar2):** PMvar2 is based on composite indicator of tissue viability, 'v final' (vfin)

Establishment of composite indicator 'vfin'		Theoretical range of values for vfin	→	Criteria	Sub-category predicted
If v3<50	→ vfin = v3	[0; 50[		vfin<y	Cat. 1A
If v3≥50 AND v60<15	→ vfin = v3+v60	[50; 115[		y≤vfin<z	Cat. 1B/1C
If v3≥50 AND v60≥15	→ vfin = (2 × v3)+v60	[115; 300[		vfin≥z	Non-Corrosive

## Two new Prediction Models (PM) improve the predictions of combined Category 1B/1C and overall accuracy

Results for 80 chemicals tested in EpiDerm™, SkinEthic™ and epiCS® were analysed on the basis of the two new PM. The application of **PMvar1** and **PMvar2** improved the predictive capacity of all three test methods. The prediction of Category 1B/1C chemicals improved dramatically. Overall accuracy is also significantly improved. Results are presented below for one of these test methods.

### Original Prediction Model

In vivo results	In vitro results PM included in TG 431			
	80 chemicals tested 3 times			
	1A	1B/1C	NC	
1A	33 (91.7%)	3 (8.3%)	0 (0.0%)	36
1B/1C	39 (41.9%)	54 (58.1%)	0 (0.0%)	93
NC	3 (2.70%)	26 (23.4%)	82 (73.9%)	111
	75	83	82	240
Accuracy = 70.4%				

### Prediction Model, Variation 1

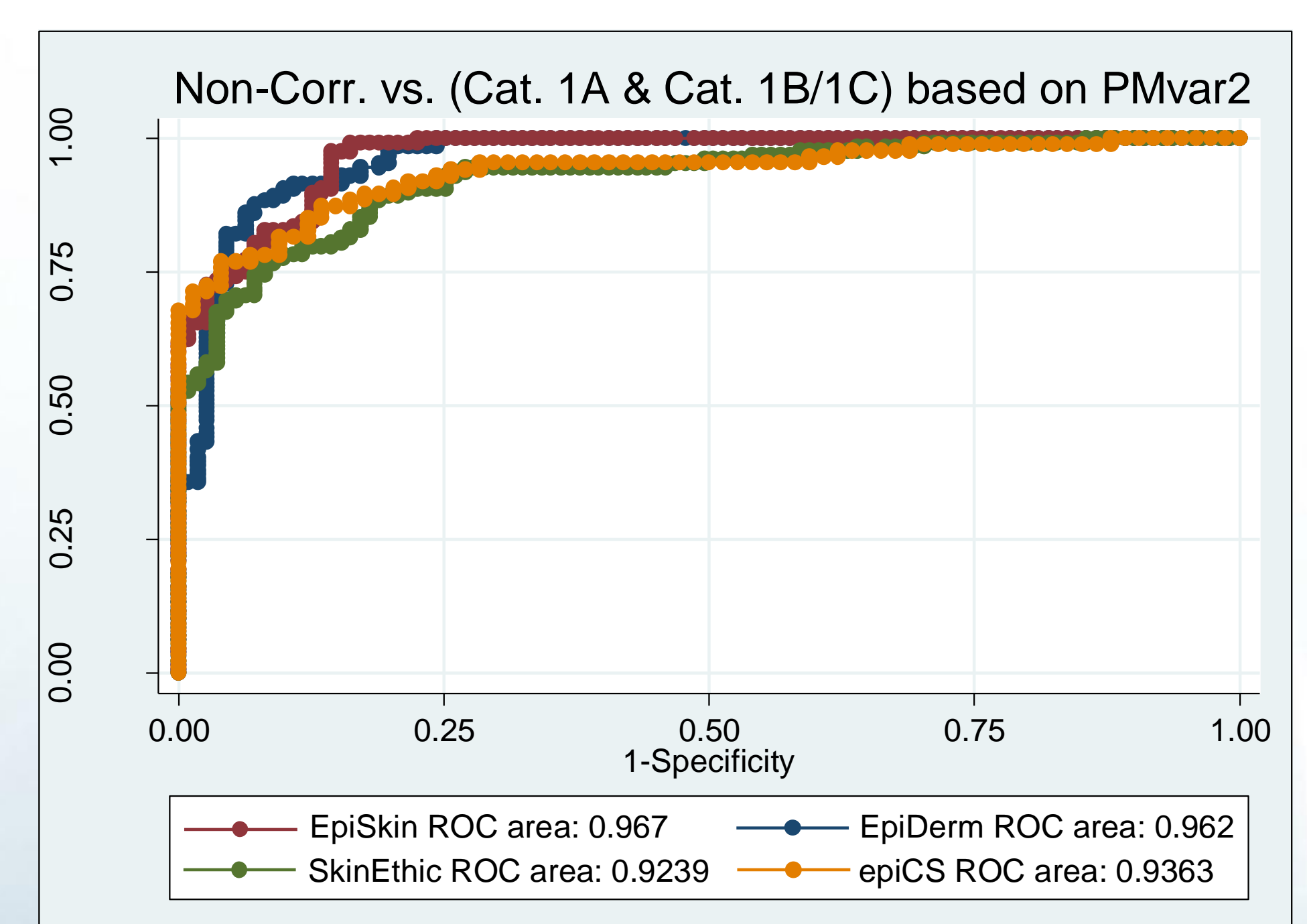
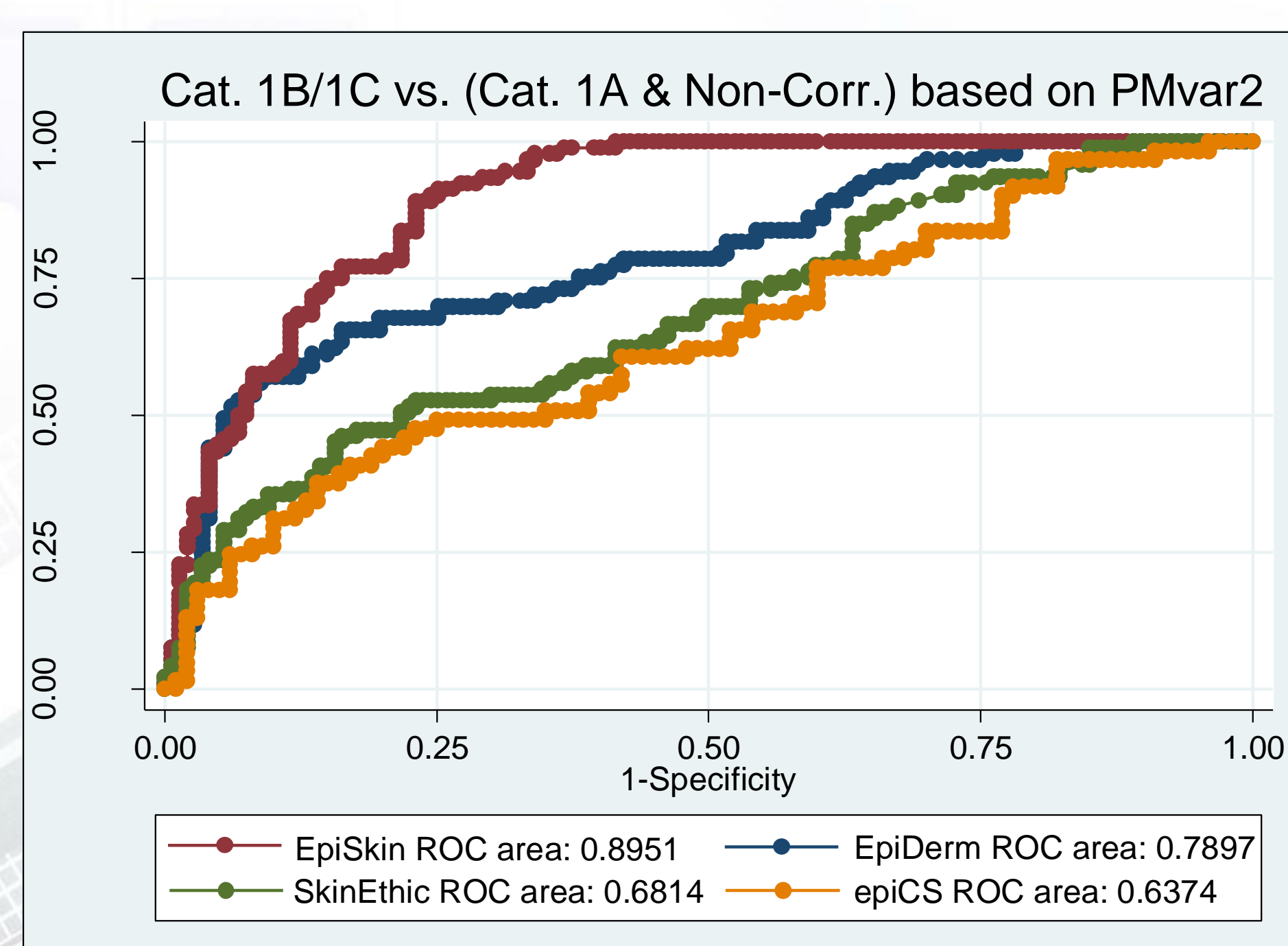
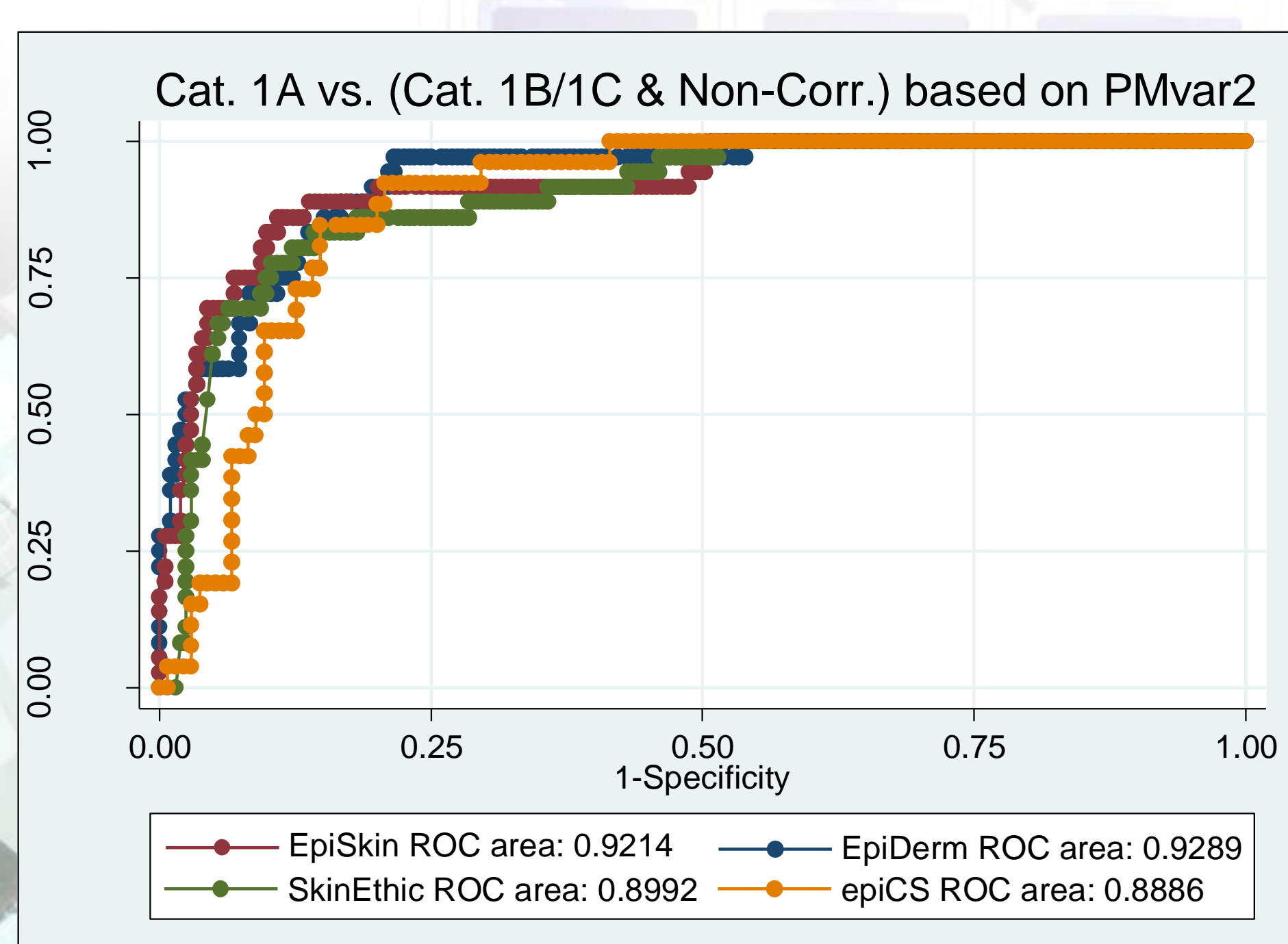
In vivo results	In vitro results using two-step			
	PMvar1 with x=20 or 30			
	1A	1B/1C	NC	
1A	28 (77.8%) 30 (83.3%)	8 (22.2%) 6 (16.7%)	0 (0.0%) 0 (0.0%)	36
1B/1C	23 (24.7%) 28 (30.1%)	70 (75.3%) 65 (69.9%)	0 (0.0%) 0 (0.0%)	93
NC	2 (1.8%) 3 (2.7%)	27 (24.3%) 26 (23.4%)	82 (73.9%) 82 (73.9%)	111
	53 61	105 97	82 82	240
Accuracy = 75.0% Accuracy = 73.8%				

### Prediction Model, Variation 2

In vivo results	In vitro results using composite tissue viability			
	PMvar2 with y=20 or 25, z=115			
	1A	1B/1C	NC	
1A	28 (77.8%) 30 (83.3%)	8 (22.2%) 6 (16.7%)	0 (0.0%) 0 (0.0%)	36
1B/1C	23 (24.7%) 27 (29.0%)	70 (75.3%) 66 (71.0%)	0 (0.0%) 0 (0.0%)	93
NC	2 (1.8%) 3 (2.7%)	27 (24.3%) 26 (23.4%)	82 (73.9%) 82 (73.9%)	111
	53 60	105 98	82 82	240
Accuracy = 75.00% Accuracy = 74.2%				

## PMvar2 allows for the generation of ROC curves from its single composite tissue viability indicator

ROC curves provide an excellent overview of test method performance and are the perfect tool for comparing the performance of different test methods (Area Under the ROC Curve)



## Conclusions:

- Best choice of cut-offs depends on objective, e.g. better accuracy, maximize Cat. 1A correct predictions, etc.
- PMvar2 and PMvar1 better than current PM, with methods achieving similar predictive capacity as EpiSkin™ for Cat. 1A vs. Cat. 1B/1C vs. Non-Corrosive
- Easier to interpret results from a single composite tissue viability indicator (PMvar2) than from two independent tissue viability values (PMvar1)

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