

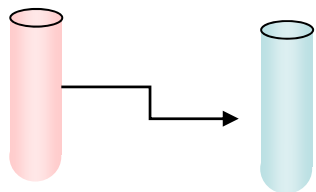


# The Phenomenome Pre-Colonoscopy GTA Blood Screening Test:

## Rapid Summary

# High Throughput, Quantitative Analysis

Serum      Extract GTAs

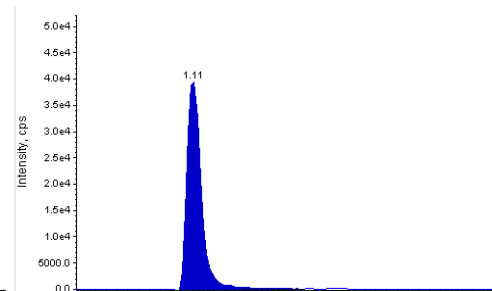
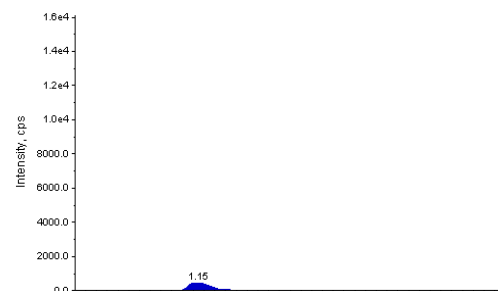


Inject

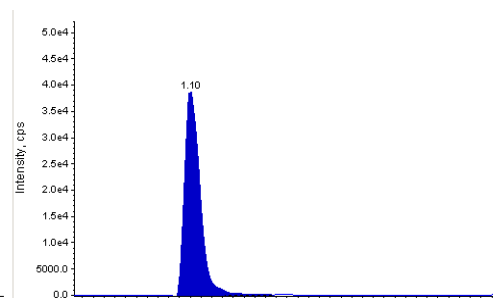
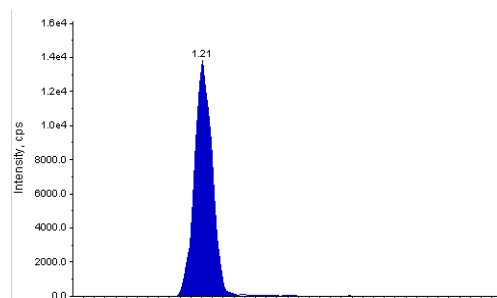


GTA

Internal Standard



CRC






Normal

Run Time: <2min

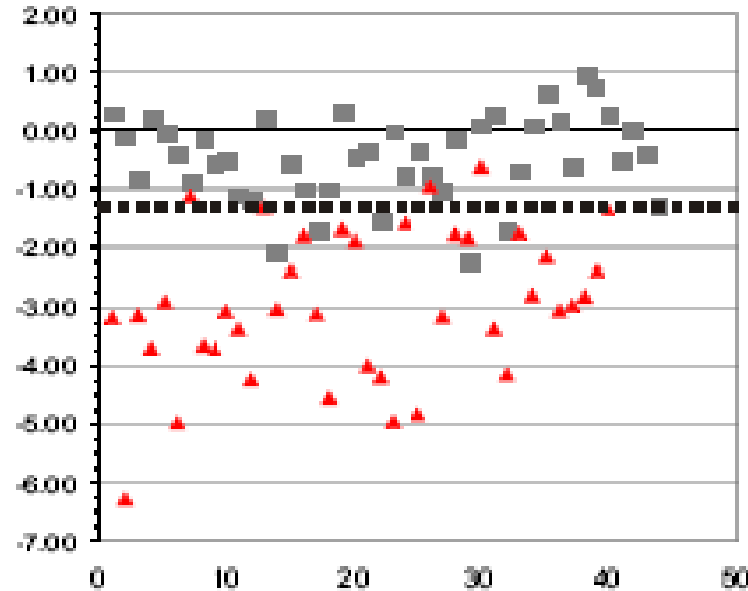
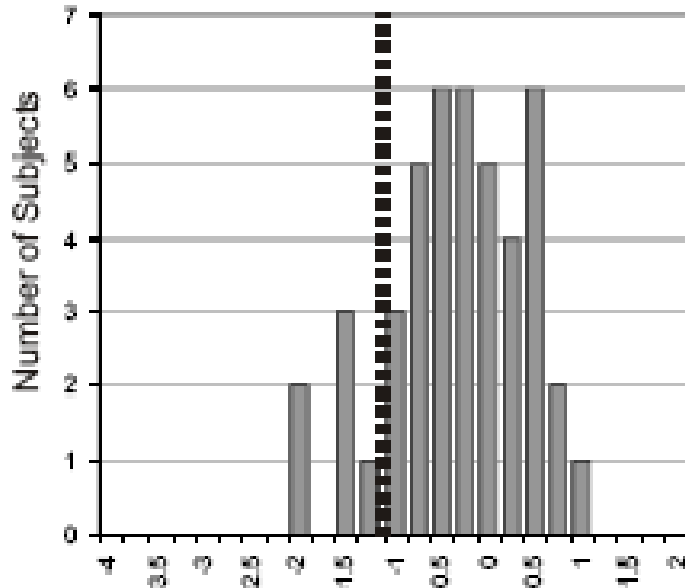
# Simple, Easy To Understand Output

Analyte	Accurate Mass	Formula	MRM Transitions
GTA1	446.3413	C28H46O4	445.4 / 383.4
GTA2	448.3565	C28H48O4	447.4 / 385.4
GTA3	450.3735	C28H50O4	449.4 / 405.4

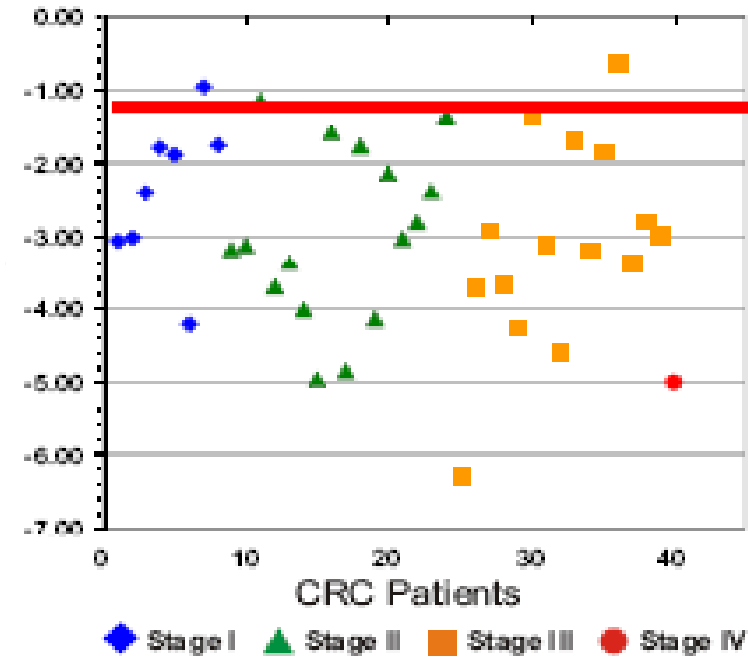
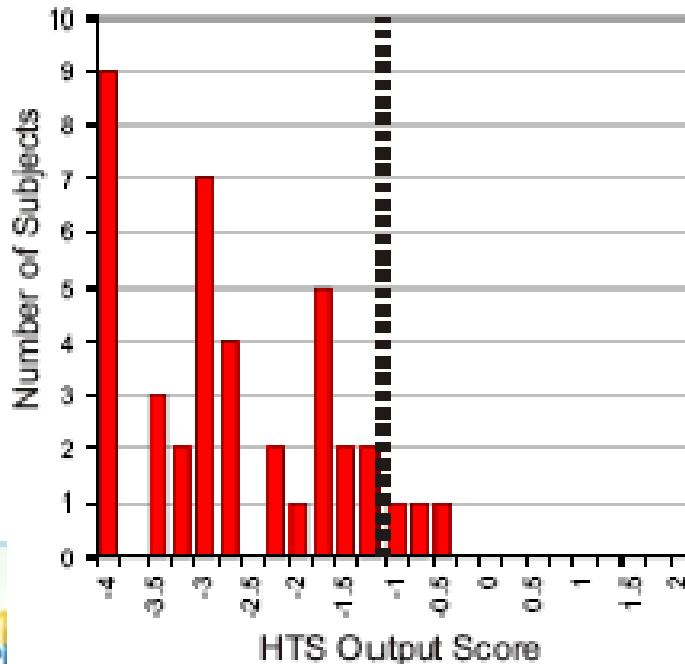
C28 marker	Scale	Concentration (ug/ml CAE)	Cut-off (ug/ml CAE)	Below Cut-off
C28H46O4		0.083	0.166	YES
C28H48O4		0.090	0.196	YES
C28H50O4		0.890	0.767	NO
<b>Recommend Colonoscopy</b>				<b>YES</b>

# LC-MS/MS Results for Original 90 Subjects

Specificity: 96%



Sensitivity: 85%



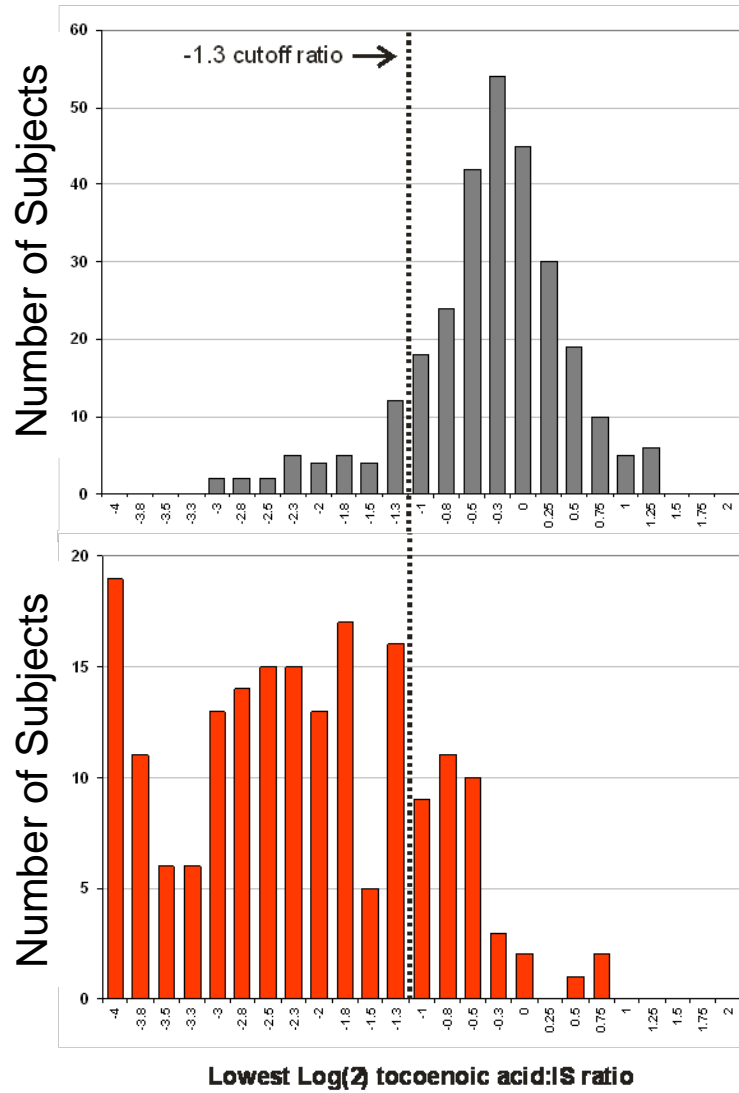


## Study #2

### Independent Case Control Study:

288 Healthy Controls  
(NOT Colonoscopy confirmed)

186 CRC  
(pre-treatment)

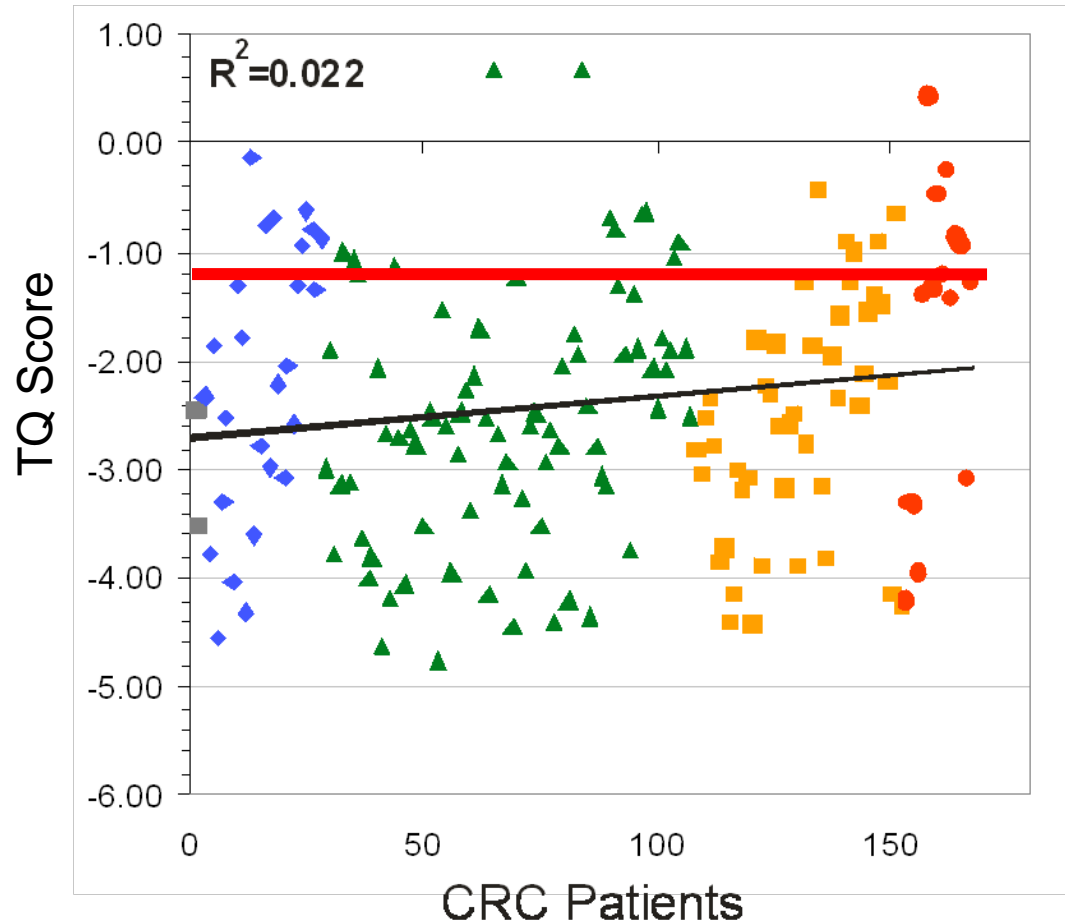


Normal Distribution

90% Specificity  
77% Sensitivity

CRC Distribution

# No Effect of Disease Stage on Biomarkers



Sensitivities:

Stage 0/I:	74%
Stage II:	84%
Stage III:	84%
Stage IV:	53%

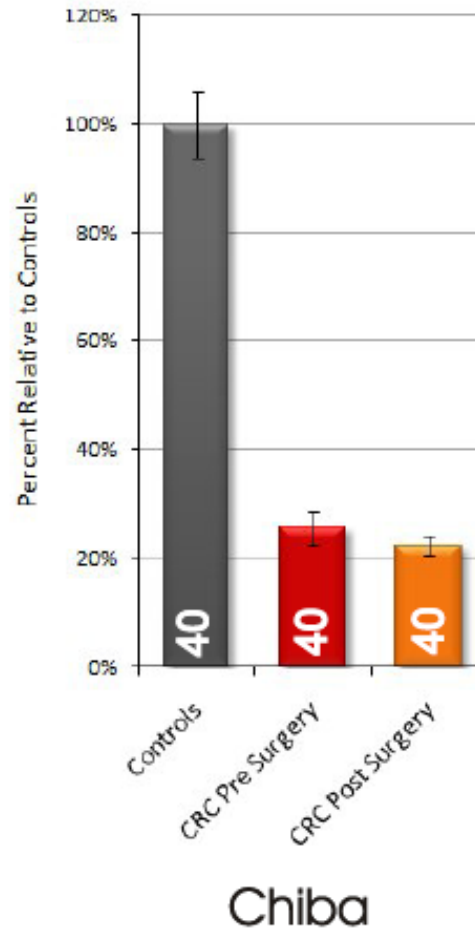
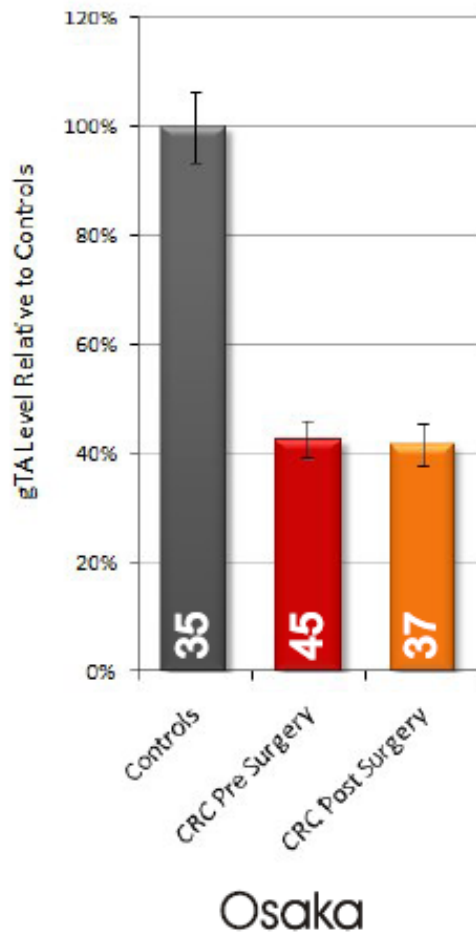
■ Stage 0    ◆ Stage I    ▲ Stage II  
■ Stage III    ● Stage IV

Why no Stage Effect?!



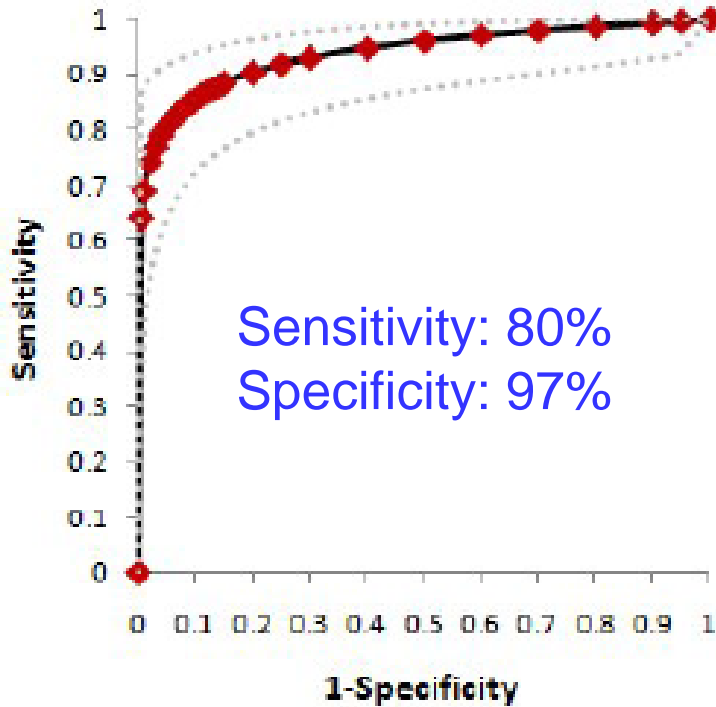
Clinical Validations #3+4:  
Independent Case Control Studies:  
**Pre- Versus Post-Surgery Evaluations**

# No Effect of Surgical Removal

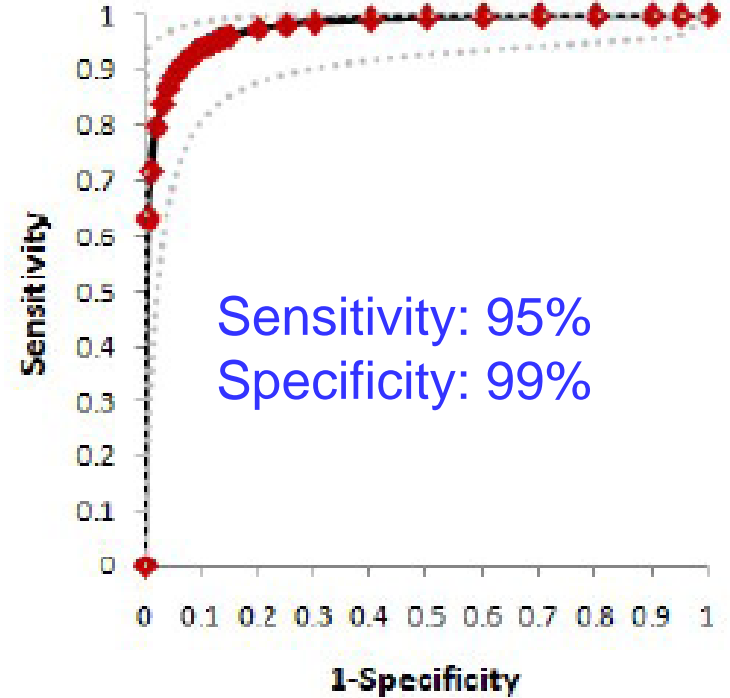


# Diagnostic Accuracy:

Osaka Pre-Surgery



Chiba Pre-Surgery



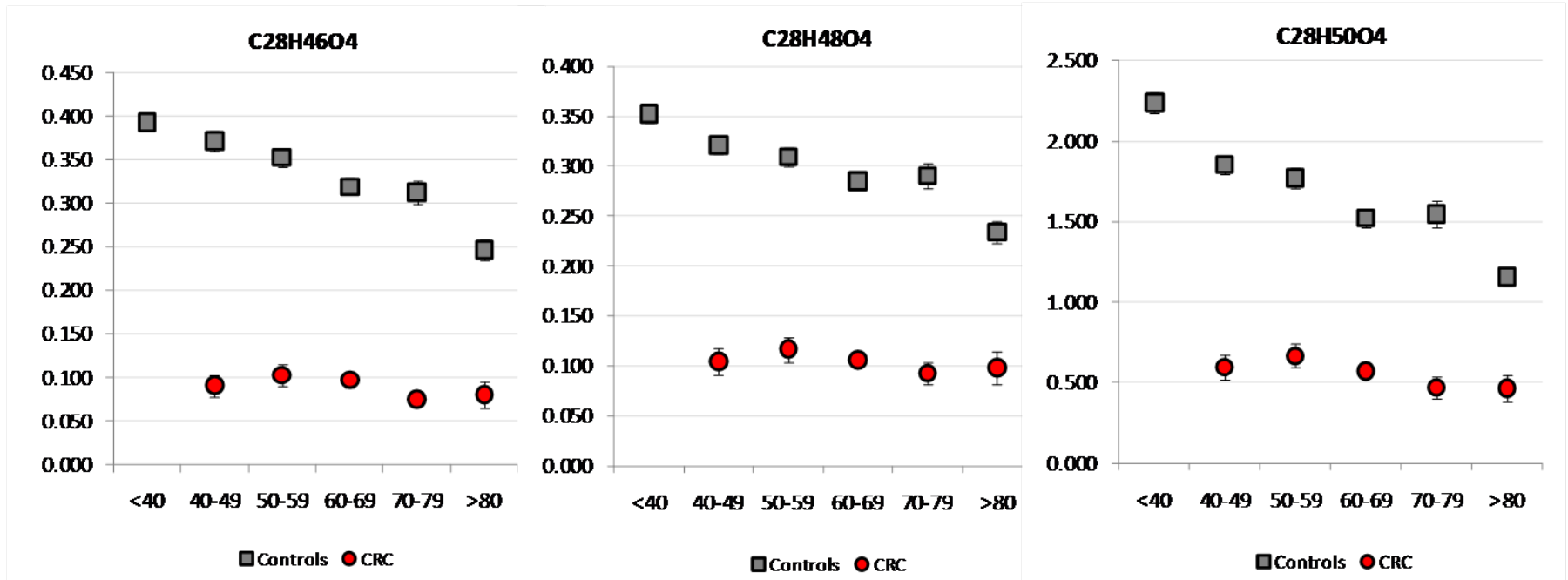


# Effect of Age on Serum GTA Levels in Healthy Normals and CRC Positive Subjects

# Study Population

	SDCL Control Group	CRC Group
Total Subjects	990	150
Male N	320	75
Male Age Range (yrs)	6-93	<b>33-91</b>
Female N	670	75
Female Age Range (yrs)	11-99	31-89
Stage 0/I	NA	12
Stage II	NA	30
Stage III	NA	46
Stage IV	NA	42
Unknown	NA	20

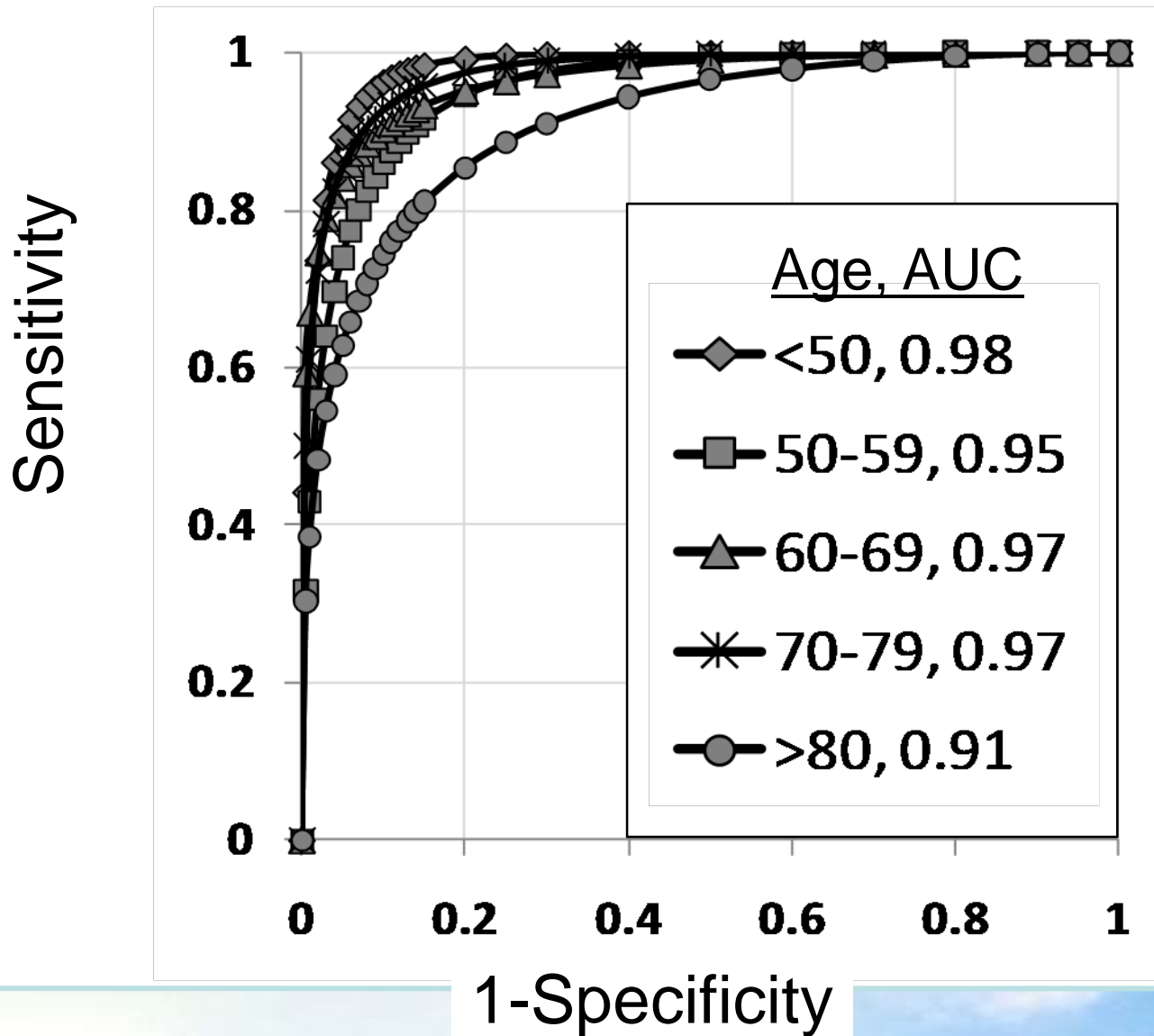
# Effect of Age: CRC Versus Non-CRC



	Female Control			Male Control		
	C28H4604	C28H4804	C28H5004	C28H4604	C28H4804	C28H5004
<b>Multiple R</b>	0.26	0.24	0.36	0.38	0.36	0.41
<b>F</b>	48.4	40	101.1	55	48	64.3
<b>P-value</b>	8.40E-12	5.20E-10	3.12E-22	1.20E-12	2.38E-11	2.09E-14

All CRC		
C28H4604	C28H4804	C28H5004
0.11	0.09	0.2
1.8	1.4	6
1.80E-01	2.30E-01	2.00E-02

# Effect of Age: AUC



# GTA Summary: CRC Screening

- **In 5 Independent case-control studies, the GTA test showed good sensitivity and specificity at all stages of CRC:**
  - Stage I: 87, 74, 94%;
  - Stage II: 84, 88, 97%;
  - Stage III: 87, 84, 100%;
  - Stage IV: 53, 100, 100%
- **Specificity: 96, 90, 97, 99%**
- **Serum GTA LC-MS/MS test has been cleared for sale in Canada**
- **The distribution and marketing of this test has been licensed to a leading Canadian diagnostic company**
- **Canadian multi-center colonoscopy trial is nearly complete ;**
- **Nationwide availability is expected by Q3/2010**
- **Licensing discussions in other geographical regions is underway.**

# CRC Clinical Trial Progress

## Multi-Center Open Enrolment Colonoscopy Trial

As of 15 April, 2010:

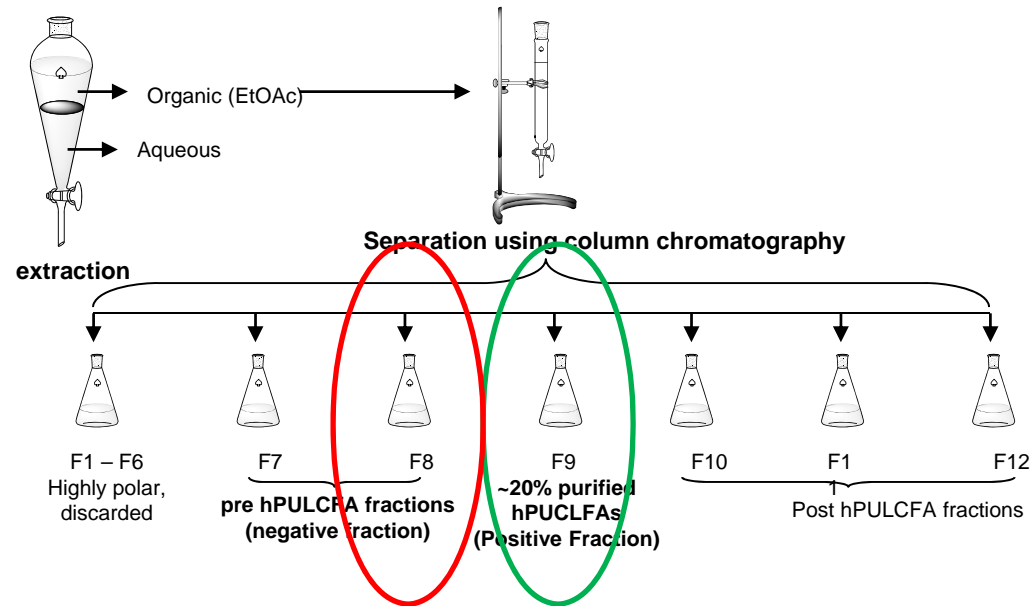
- 4,400 subjects enrolled (+1000 Random, Non-Colonoscopy Controls)
- ~60 New CRC<sup>+</sup> subjects (>100 By Late Summer)
- >150 Previously diagnosed CRC<sup>+</sup>



# Clinical Biomarkers: Disease Mechanisms (*In Vivo* to *In Vitro* Translation)

(CRC)

# Isolation of CRC Biomarkers from Human Serum

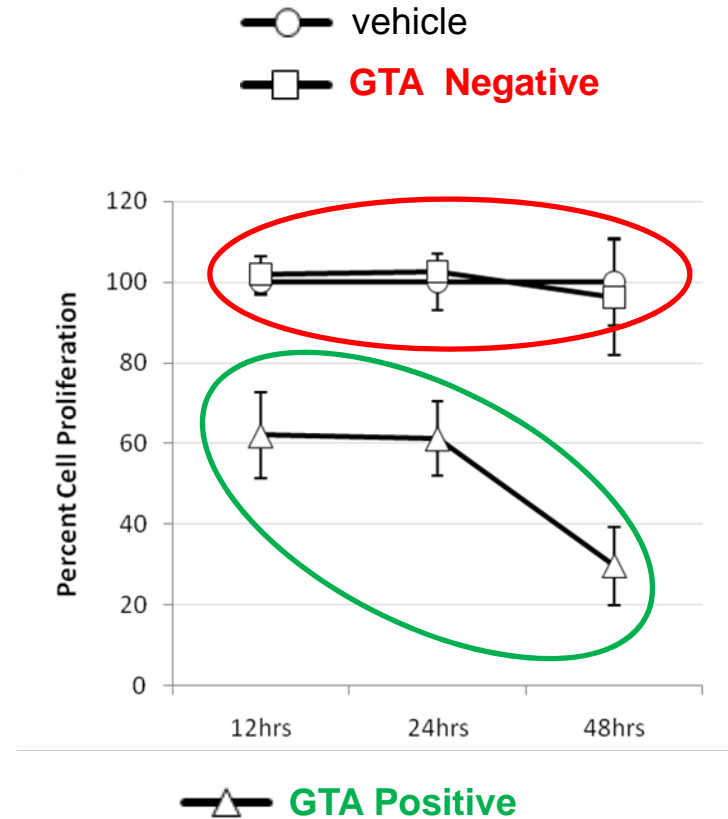
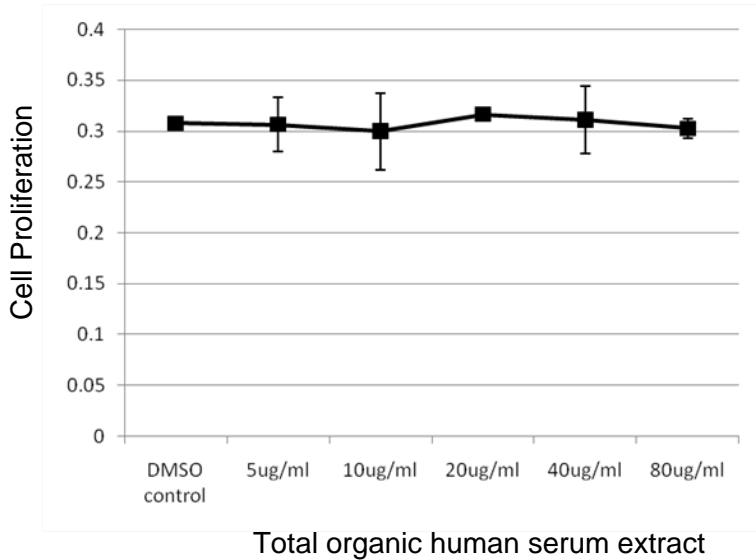


**GTA Negative (F8)**

**GTA Positive (F9)**

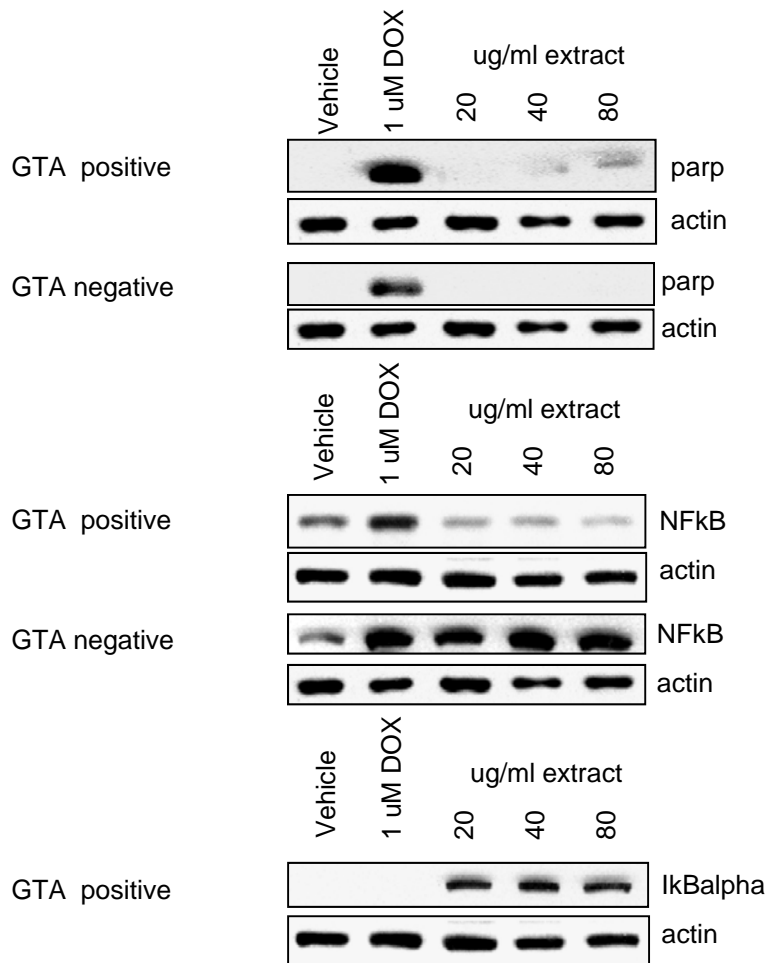
# Effect on Cell Proliferation

48 hours



**GTAs have Anti-Proliferative Activity**

# Cancer-Related Intracellular Signalling



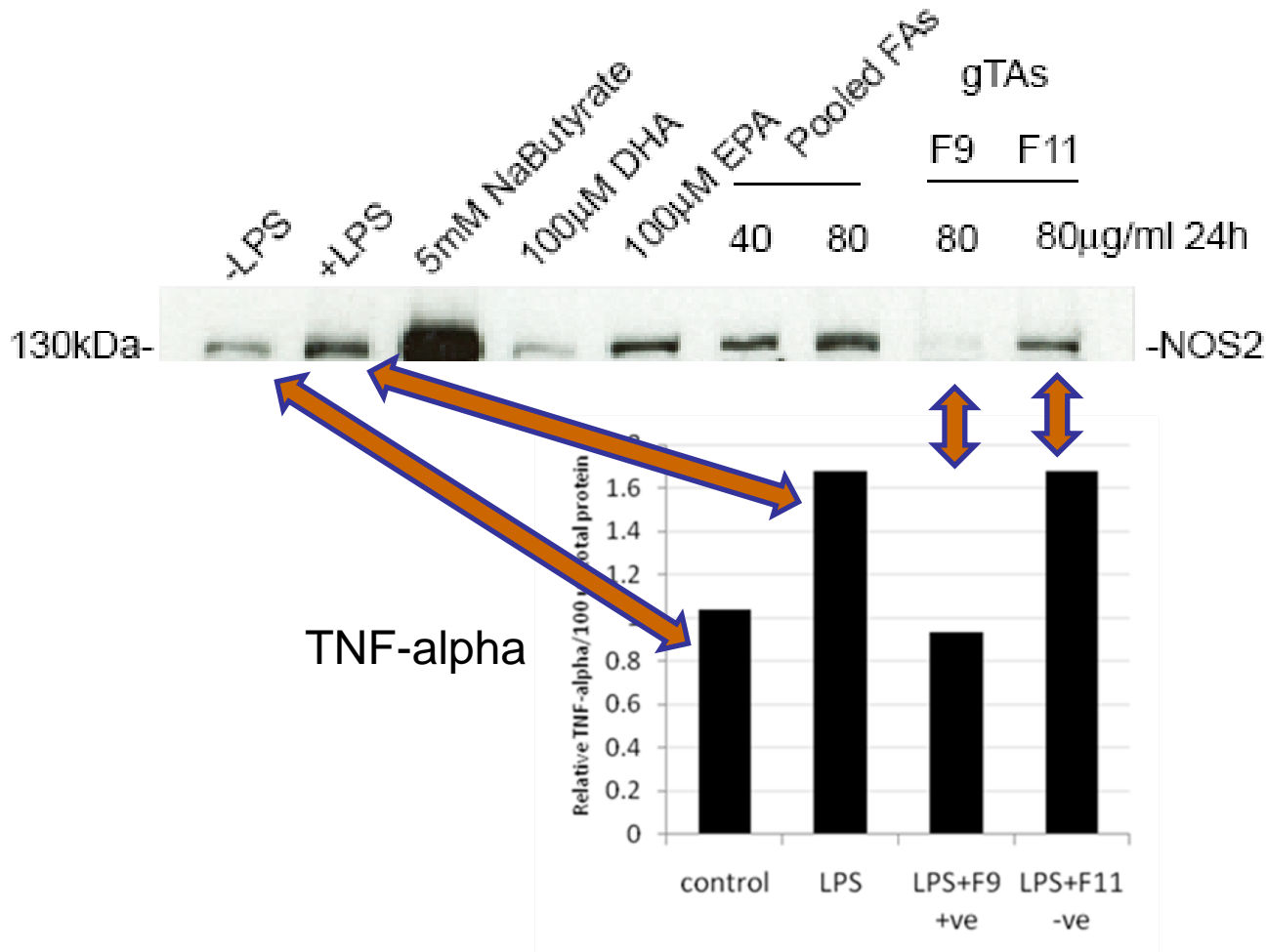
**Like** Doxorubicin, GTAs are pro-Apoptotic (parp induction)

**Unlike** Doxorubicin, GTAs are Anti-Inflammatory, not Pro-inflammatory: Inhibition of NFkB

Mechanism of NFkB inhibition is via IkbAlpha induction

**GTAs are endogenous pro-Apoptotic, anti-inflammatory agents**

# Cancer-Related Intracellular Signaling



**GTAs Completely Block LPS Mediated Inflammation**

# GTA Summary: Causal Mechanisms and Therapeutic Intervention

- **GTA Deficiency may be causal:**
  - No stage effect
  - No effect of tumor burden
  - Age-associated decrease
  - GTAs are anti-inflammatory
  - GTAs are pro-apoptotic
  - GTAs are anti-proliferative
- **Synthetic Chemistry and Formulation Studies of an Orally Bioavailable GTA Pro-Drug are Ongoing**